

# ANNALS OF INTERNAL MEDICINE

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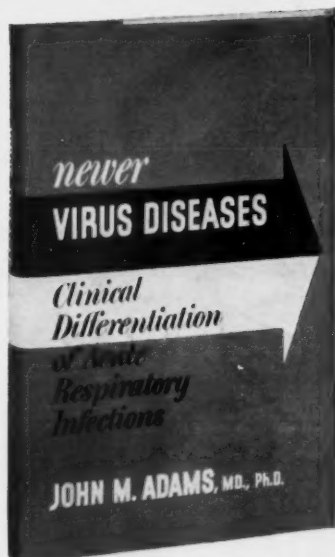
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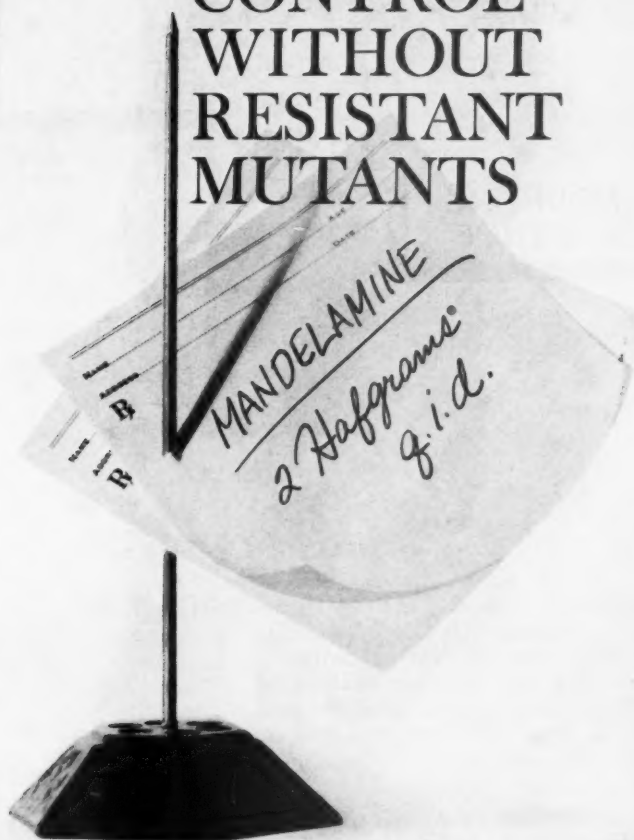
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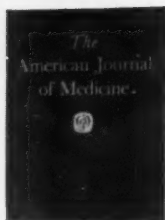
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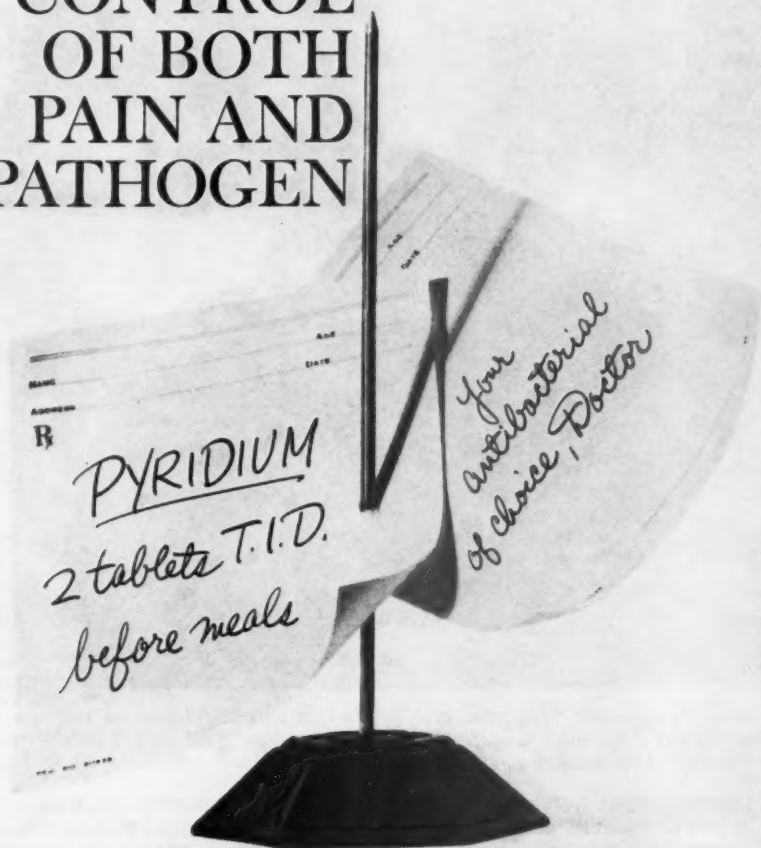
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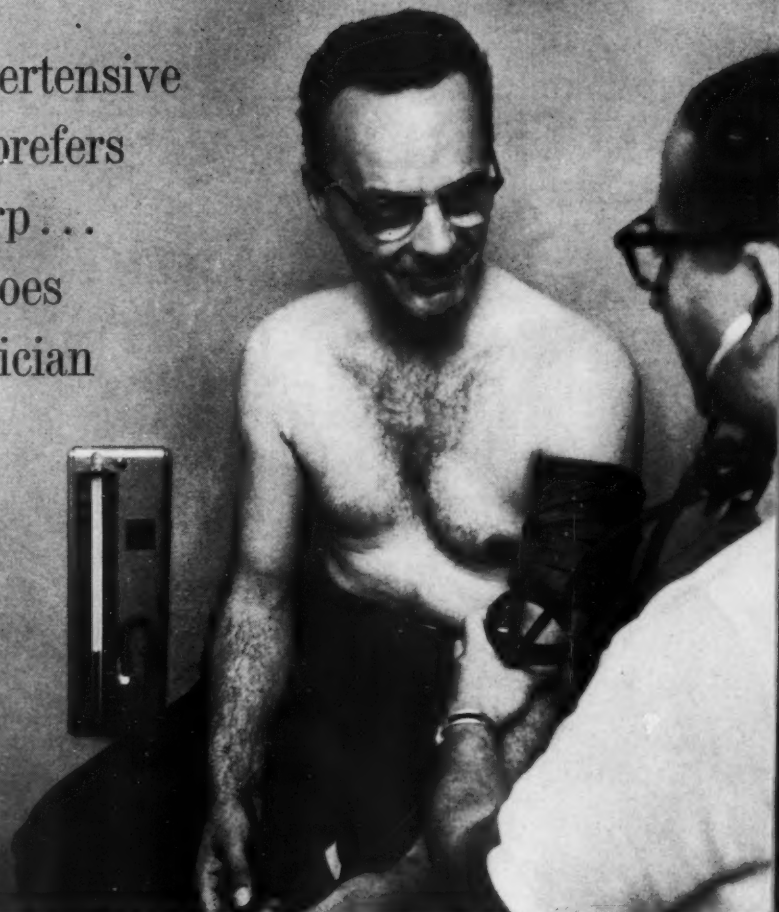


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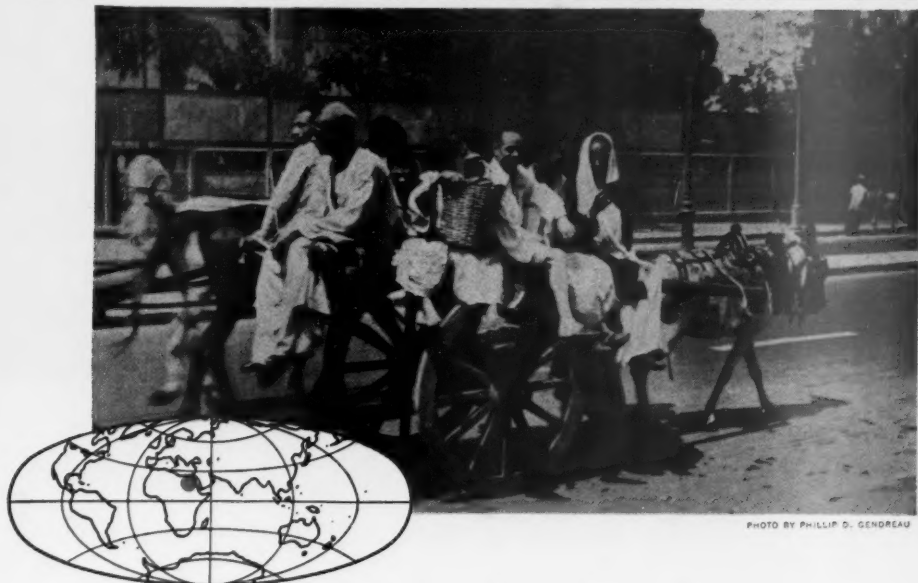


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6. Friedman, A. P.: *Ann. N. Y. Acad. Sc.* 67:822, May 9, 1957. 7. Greenberg, L. A. *et al.*: *Ann. N. Y. Acad. Sc.* 67:816, May 9, 1957. 8. Holliday, A. R.: *Northwest Med.* 58:837, June 1959. 9. Hollister, L. E. *et al.*: *Dis. Nerv. System* 17:289, Sept. 1956. 10. Laird, D. M. *et al.*: *Dis. Nerv. System* 18:346, Sept. 1957.



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Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets. Also as MEPROTABS®—400 mg. unmarked, coated tablets; and as MEPROSPAN®—400 mg. and 200 mg. continuous release capsules.*

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.....[double-blind]

11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. 12. Muhlfeider, W. J. et al.: Dis. Nerv. System 20:587, Dec. 1959. 13. Pollak, M.: Practitioner 184:231, Feb. 1960. 14. Rickels, K. et al.: J.A.M.A. 171:1649, Nov. 21, 1959. 15. Rustek, H. I.: Am. J. Cardiol. 3:547, April 1959. 16. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

## Miltown®

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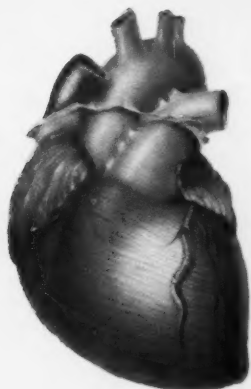
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#### IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



#### AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

## Protects your coronary patient better than vasodilation alone

**Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.**

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important — Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

**Supplied:** Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

**Dosage:** 1 or 2 tablets q.i.d. before meals and at bedtime, according to individual requirements.

#### REFERENCES

1. Ellis, L. B. *et al.*: *Circulation* 17:945, May 1958.
2. Friedlander, H. S.: *Am. J. Cardiol.* 1:395, Mar. 1958.
3. Riseman, J.E.F.: *New England J. Med.* 261:1017, Nov. 12, 1959.
4. Russek, H. I. *et al.*: *Circulation* 12:169, Aug. 1955.
5. Russek, H. I.: *Am. J. Cardiol.* 3:547, April 1959.
6. Tortora, A. R.: *Delaware M. J.* 30:298, Oct. 1958.
7. Waldman, S. and Felner, L.: *Am. Pract. & Digest Treat.* 8:1075, July 1957.

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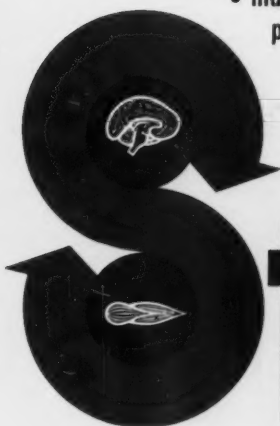
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# a new, improved, more potent relaxant for anxiety and tension

- effective in half the dosage required with meprobamate
- much less drowsiness than with meprobamate, phenothiazines, or the psychosedatives
- does not impair intellect, skilled performance, or normal behavior
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# Striatran

*alert tranquillity*

EMYLCAMATE®

- a familiar spectrum of antianxiety and muscle-relaxant activity
- no new or unusual effects—such as ataxia or excessive weight gain
- may be used in full therapeutic dosage even in geriatric or debilitated patients
- no cumulative effect
- simple, uncomplicated dosage, providing a wide margin of safety for office use

STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

**Adult Dosage:** One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

**Supply:** 200 mg. tablets, coated pink, bottles of 100.

While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services,  
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COUMADIN is the *original and only* warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.<sup>1,2</sup>



Over 101,000,000 doses  
administered to date...



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*Full range of oral and parenteral dosage forms*—COUMADIN® (warfarin sodium) is available as: *Scored tablets*—2 mg., lavender; 5 mg., peach; 7 1/2 mg., yellow; 10 mg., white; 25 mg., red. *Single Injection Units*—one vial, 50 mg., and one 2-cc. ampul. *Water for Injection*—one vial, 75 mg., and one 3-cc. ampul.

*Average Dose:* Initial, 40-60 mg. For elderly and/or debilitated patients, 30-30 mg. *Maintenance:* 5-10 mg. daily, as indicated by prothrombin time determinations.

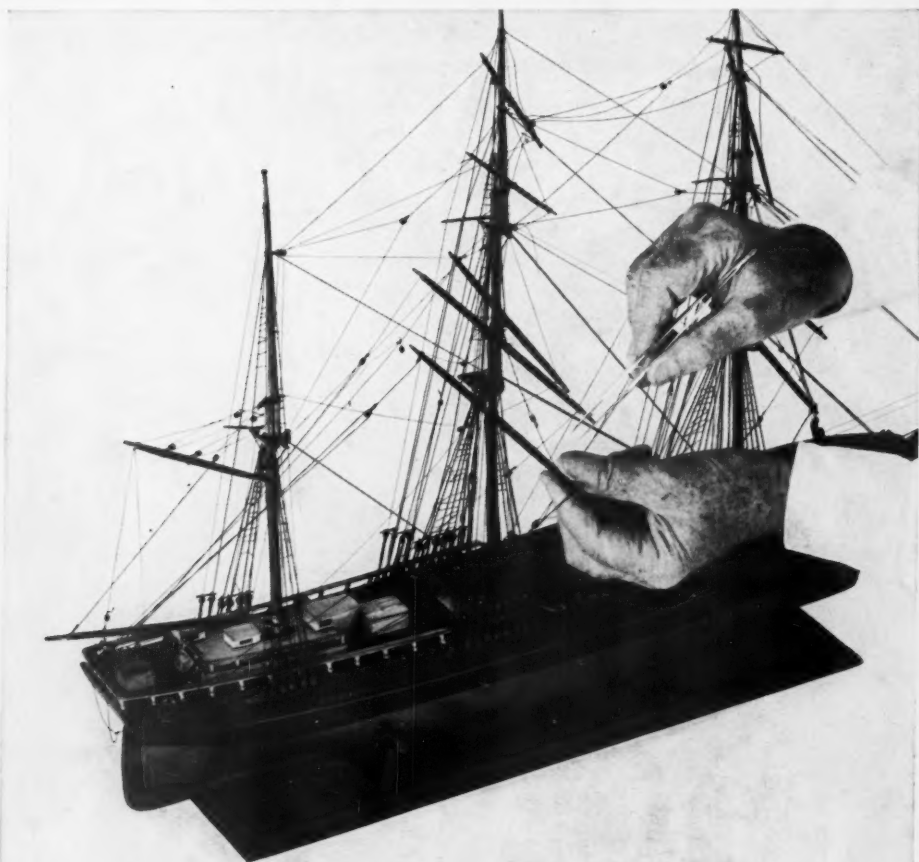
*Source:* S. L. et al., J.A.M.A. 167:104, June 7, 1958; 2. Miller, R. M., Disease a Month, Chicago, Yr. 84, 1960, Mar., 1960, p. 13.

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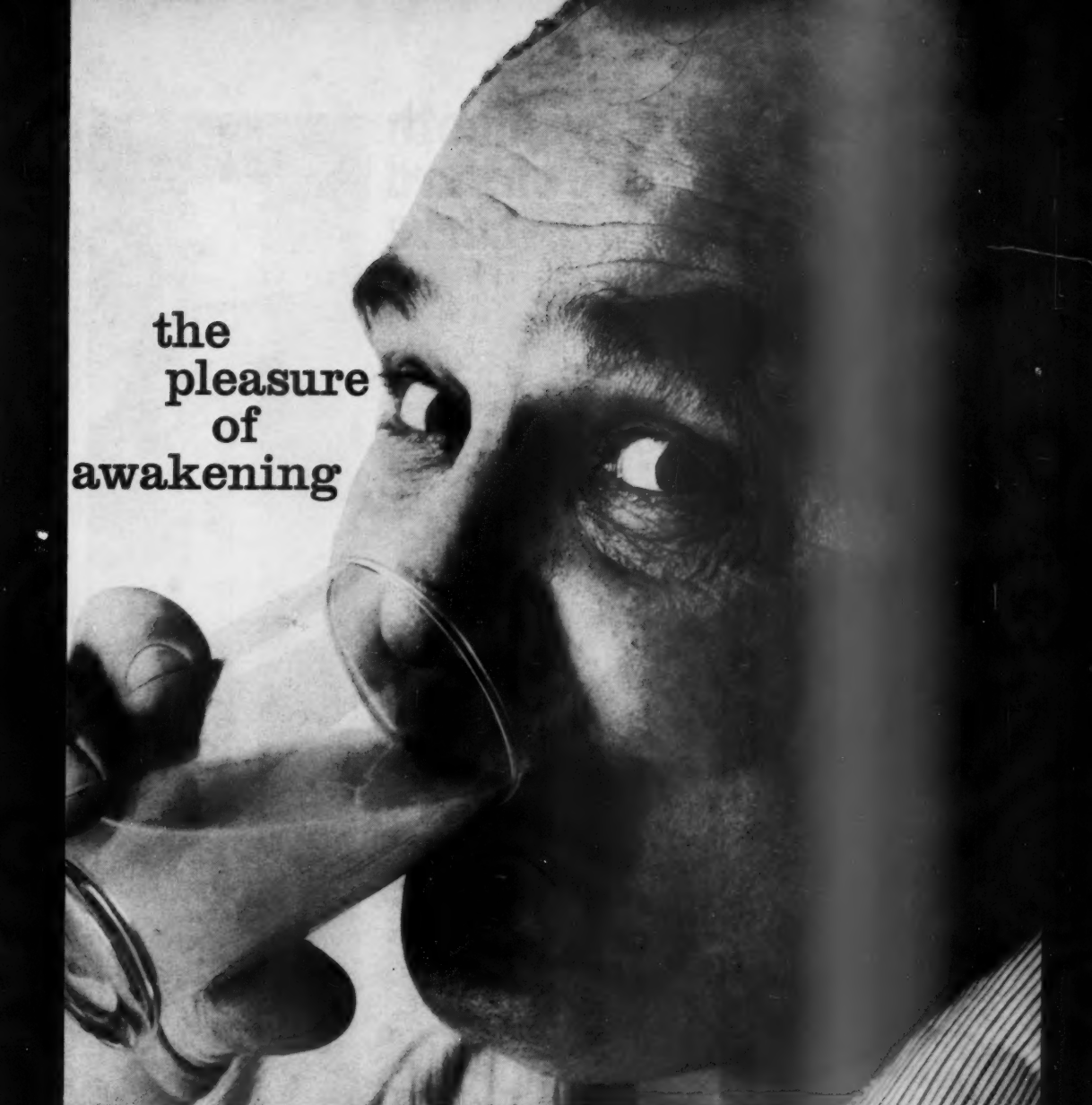
## PARKINSONISM



1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.

2. Schwab, R. S.: *Geriatrics* 14:545 (Sept.) 1959.

3. Doshay, L. J. et al.: *J.A.M.A.* 160:348 (Feb. 4) 1956.



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**"I slept like a log"**

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300-mg capsules



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A vertical ruler with a scale from 0 to 100 cm, used for measurement. The ruler is marked in centimeters and millimeters. A dark vertical line is drawn across the ruler, indicating a measurement of approximately 50 cm.

**New Rautrax-N results in prompt lowering of blood pressure.\*** Rautrax-N, a new antihypertensive-diuretic preparation, provides improved therapeutic action<sup>1</sup> plus enhanced diuretic safety for all degrees of essential hypertension. A combination of Raudixin and Naturetin, Rautrax-N facilitates the management of hypertension when rauwolfia alone proves inadequate, or when prolonged treatment, with or without associated edema, is indicated.

Naturetin, the diuretic of choice, also possesses marked antihypertensive properties, thus complementing the known antihypertensive action of Raudixin. In this way a lower dose of each component in Rautrax-N controls hypertension effectively with few side effects and a greater margin of safety.<sup>1-16</sup>

Other advantages are a balanced electrolyte pattern<sup>1-16</sup> and the maintenance of a favorable urinary sodium-potassium excretion ratio.<sup>2-16</sup> Clinical studies<sup>1-9</sup> have shown that the diuretic component of Rautrax-N—Naturetin—has only a slight effect on serum potassium. The supplemental potassium chloride provides additional protection against potassium depletion that may occur during long term therapy.

Rautrax-N may be used independently or with other antihypertensive drugs, such as ganglionic blocking agents, veratrum or hydralazine, when needed for the occasionally difficult patient.

**Supply:** Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin (Squibb Rauwolfia Serpentina Whole Root) and 4 mg. Naturetin (Squibb Benzydrolflumethiazide), with 400 mg. potassium chloride.

**Dosage:** For initial therapy, the suggested dosage is 1 to 4 Rautrax-N tablets daily after meals. If the higher amounts are needed, daily dosage should be divided into 2 doses given every 12 hours. However, dosage should be initiated at a low level, which may be increased after intervals of several days, if necessary, until the desired response is obtained. For maintenance therapy, 1 or 2 Rautrax-N tablets daily should prove adequate; however, daily maintenance dosage may range from 1-4 Rautrax-N tablets. **Note:** In hypertensive patients already on ganglionic blocking agents, veratrum or hydralazine, the addition of Rautrax-N will require an immediate dosage reduction of each of these agents by at least 50 per cent. The same dosage reduction applies when any of these agents is added to the Rautrax-N regimen. Literature available on request.

**References:** 1. Reports to the Squibb Institute, 1960. 2. David, N. A.; Porter, G. A., and Gray, R. H.: *Monographs on Therapy* 5:60 (Feb.) 1960. 3. Stenberg, E. S., Jr.; Benedetti, A., and Forsham, P. H.: *Op. cit.* 5:46 (Feb.) 1960. 4. Fuchs, M.; Moyer, J. H., and Newman, B. E.: *Op. cit.* 5:55 (Feb.) 1960. 5. Marriott, H. J. L., and Schamroth, L.: *Op. cit.* 5:14 (Feb.) 1960. 6. Ira, G. H., Jr.; Shaw, D. M., and Bogdonoff, M. D.: *North Carolina M. J.* 21:19 (Jan.) 1960. 7. Cohen, B. M.: *M. Times*, to be published. 8. Breneman, G. M. and Keyes, J. W.: *Henry Ford Hosp. M. Bull.* 7:281 (Dec.) 1959. 9. Forsham, P. H.: *Squibb Clin. Res. Notes* 2:5 (Dec.) 1959. 10. Larson, E.: *Op. cit.* 2:10 (Dec.) 1959. 11. Kirkendall, W. M.: *Op. cit.* 2:11 (Dec.) 1959. 12. Yu, P. N.: *Op. cit.* 2:12 (Dec.) 1959. 13. Weiss, S.; Weiss, J., and Weiss, B.: *Op. cit.* 2:13 (Dec.) 1959. 14. Moser, M.: *Op. cit.* 2:13 (Dec.) 1959. 15. Kahn, A., and Grenblatt, I. J.: *Op. cit.* 2:15 (Dec.) 1959. 16. Grollman, A.: *Monographs on Therapy* 5:1 (Feb.) 1960.

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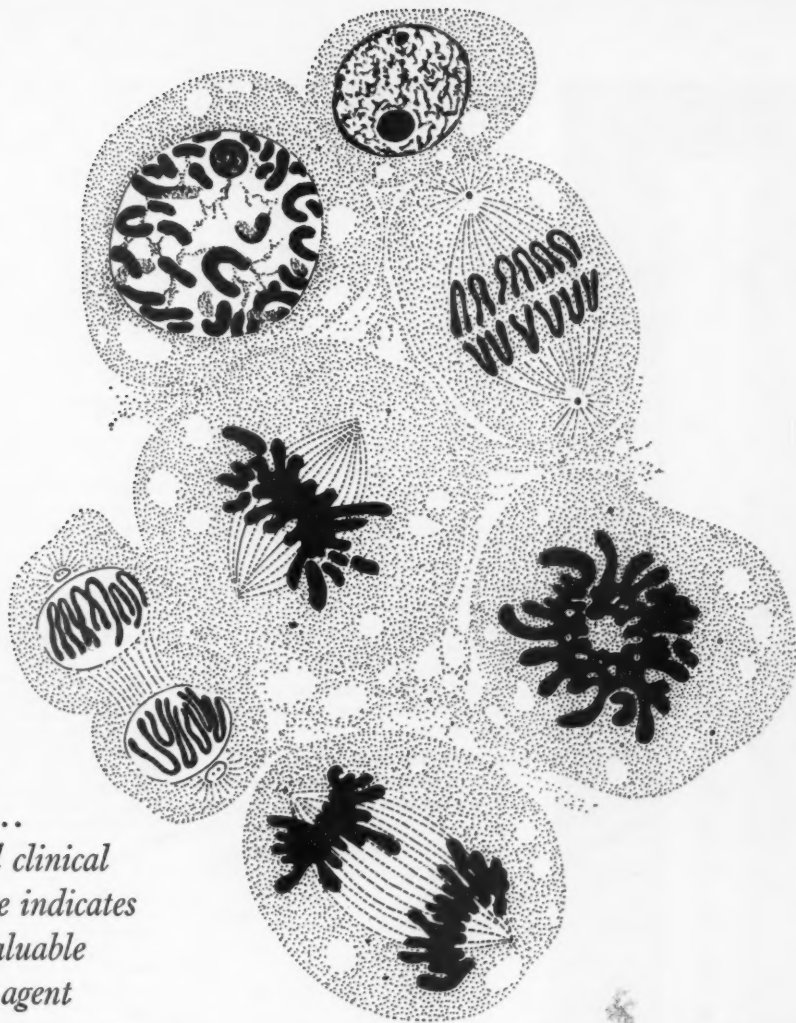
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Report from a recent comparative clinical evaluation of two alkylating agents: "With the use of cyclophosphamide [Cytosan], there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."<sup>\*</sup>

Other Advantages in Clinical Practice: Broad spectrum of application • High therapeutic index • No vesicant activity—may be given orally or parenterally.

For a copy of the Cytosan brochure, or other additional information on Cytosan, communicate directly with the Medical Department (Section B), Mead Johnson & Company, Evansville 21, Indiana.

<sup>\*</sup>Papac, R.; Petrakis, N. L.; Amini, F. and Wood, D. A.: J.A.M.A. 172:1387-1391 (March 26) 1960.

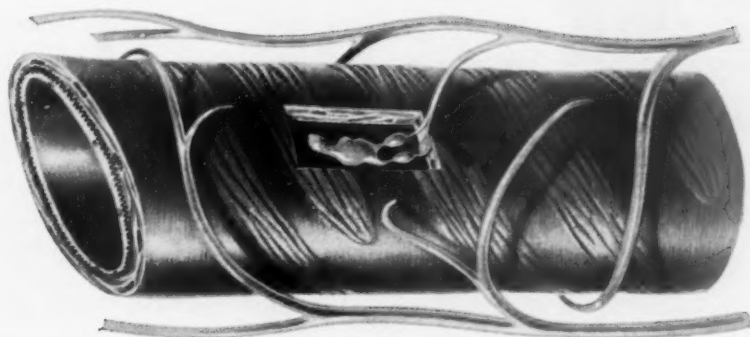


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*Symbol of service in medicine*



*New principle: antihypertensive action at  
nerve-arteriole junction*

**ISMELIN®**



*New achievement: reduces high blood pressure to  
near-normal levels in 80 to 90 per cent of cases\**

\*In 80 to 90 per cent of patients with moderate to severe (including malignant) hypertension, Ismelin—alone or combined with other antihypertensives—reduced systolic and diastolic blood pressures to normal or near-normal levels in the standing position.<sup>1-3</sup> The illustration above—a medical artist's concept of the arteriole—shows the Ismelin site of action: the nerve-arteriole junction.

For comprehensive information about this remarkable new product of CIBA research, please see the following pages.

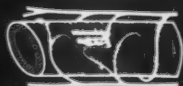
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## *New principle, new achievement in antihypertensive therapy*

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### ISMELIN



Ismelin is a potent new antihypertensive agent developed by CIBA research for moderate to severe hypertension. Ismelin represents a new principle in antihypertensive therapy: It acts at the nerve-arteriole junction where it opposes the release and/or distribution of the pressor substance, norepinephrine.

This action differs markedly from that of previously available antihypertensive agents; rauwolfia compounds, for instance, inhibit norepinephrine through the central nervous system, while ganglionic blockers interrupt transmission of pressor impulses at the level of sympathetic ganglia.

Because it acts at the site of arteriolar blood pressure regulation—with no demonstrable evidence of central or parasympathetic effect—Ismelin produces a clear-cut antihypertensive response in a high percentage of cases.

### *Advantages* **ISMELIN** *offers your hypertensive patient*

■ Almost all forms of moderate to severe hypertension can be managed with Ismelin,

alone or in combination with other antihypertensives.

■ Ismelin brings blood pressure down in many persons refractory to other antihypertensive agents.

■ Ismelin lowers blood pressure in many patients who cannot be treated effectively with other potent agents because they cannot, or will not, tolerate the side effects.

■ Ismelin controls many cases

of renal hypertension, often when other agents fail.

■ Patients need take Ismelin only once a day.

■ Most patients have been treated with Ismelin for prolonged periods without developing tolerance to it (although instances of tolerance have been reported).

■ Smooth absorption of Ismelin results in predictable blood pressure responses.

## Sites of Action: How Ismelin differs from other antihypertensive agents

**Barbiturates**—The cerebral cortex.

**Rauwolfia compounds**—The hypothalamus (with some peripheral effects).

**Hydralazine**—The midbrain. Hydralazine prevents excessive outflow of sympathetic vasopressor impulses. In addition, it inhibits release and/or action of circulating pressor substances.

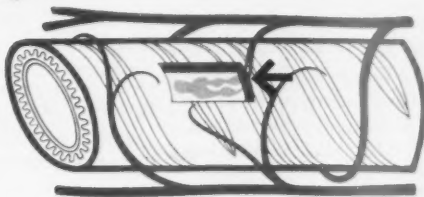
**Veratrum alkaloids**—The vasomotor center in the medulla, but acting only indirectly (act through a reflex from the carotid sinus).

**Ganglionic blocking agents**—The autonomic ganglia. Since ganglionic blockers act by blocking transmitter substance, acetylcholine, in the ganglia, these drugs also block the parasympathetic system.

**Thiazide compounds**—Specific site or mode of action still undetermined.



**ISMELIN**—Represents a new principle in the treatment of high blood pressure. Acting at the nerve-arteriole junction, Ismelin inhibits the release and/or distribution of the pressor substance, norepinephrine.



**ISMELIN:**  
*for a wide  
range of  
hypertensive  
patients*

Ismelin is useful in patients with moderate to severe hypertension—particularly:

- In place of other antihypertensive drugs when patients are refractory and blood pressure levels remain persistently high.
- In combination with other antihypertensive drugs when these fail to bring blood pressure down to desired levels, or to normotensive ranges.
- As a replacement for other potent agents (including ganglionic blockers) when side effects prevent effective treatment.

## *In 80 to 90 per cent of cases<sup>1,3</sup>...Ismelin reduces blood pressure to near-normal levels*

According to reports from more than 100 clinical investigators, Ismelin reduces blood pressure levels to normal or near-normal in a remarkably high percentage of patients. Note these typical findings:

### **17 of 18 patients (94.4%) treated with Ismelin become normotensive in the erect position.**

Page and Dustan<sup>1</sup> gave Ismelin orally, alone or in combination with other antihypertensive drugs, to 18 patients daily for 2 to 12 weeks.

**RESULTS:** All 18 patients had reductions in standing blood pressure; 16 had reductions in supine blood pressure as well. In 17 of the 18 cases, blood pressure levels became normal or near-normal in the erect position.

#### *Average Standing B.P.*

Control pressures ..... 173/115 mm. Hg  
Results with Ismelin ..... 131/85 mm. Hg  
(during last week of treatment)

### **In 14 of 15 patients (93.3%) on Ismelin, blood pressure reduced to normal or near-normal levels in the standing position.**

Ismelin was administered orally by Frohlich and Freis<sup>2</sup> for 4 to 9 weeks to 15 male patients selected from the hypertensive clinic. All previous antihypertensives were discontinued for a period of 2 weeks.

**RESULTS:** Ismelin evoked a potent antihypertensive response in the erect position: the blood pressure of 14 of the 15 patients dropped to normotensive or near-normotensive levels. "The response [to Ismelin] was characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade."<sup>2</sup>

#### *Average Standing B.P.*

Pretreatment pressures ..... 181/122 mm. Hg  
Results with Ismelin ..... 132/90 mm. Hg

### **In 15 of 18 subjects (83.3%), Ismelin reduced high blood pressure to near-normotensive levels.**

Ismelin was administered orally by Richardson and Wyso<sup>3</sup> to 18 male hospitalized patients with hypertension. Complications included hemorrhages, exudates or papilledema of the optic fundi. Ten had BUN above 25 mg. per cent "...and six had previously failed to respond to ganglionic blocking drugs and chlorothiazide in the hospital."<sup>3</sup>

**RESULTS:** "All patients showed definite reduction in blood pressure coincident with administration of Ismelin. In most of the subjects [15], standing blood pressure could be maintained near normal levels."<sup>3</sup>

#### *Average Standing B.P.*

Control pressures ..... 195/129 mm. Hg  
Results with Ismelin ..... 139/89 mm. Hg

### **"Side-effects encountered... have indeed been minimal..."<sup>4</sup>**

Brest and Moyer<sup>4</sup> state: "Side-effects [of Ismelin] encountered to date have indeed been minimal, with mild diarrhea as the only significant complaint even when large daily doses (450 mg.) of the drug are administered. No evidence of toxic action of the drug has been encountered thus far." Page<sup>5</sup> observes: "...Guanethidine [Ismelin] has the advantage [over ganglionic blockers] in that it is much easier to handle and does not produce nearly as much dose sensitivity. Too much of a ganglion-blocking agent will really 'clobber' the patient; with Guanethidine, there is much more leeway." Kirkendall and co-workers<sup>6</sup> report: "Guanethidine has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy." Leishman and associates<sup>7</sup> conclude: "The capacity of guanethidine to reduce the blood-pressure of hypertensive patients without symptoms of parasympathetic blockade is consistent with a mechanism of selective sympathetic-nerve inhibition..."

## How to use Ismelin:

**Precautions:** Ismelin is a potent drug, and its misuse can lead to disturbing and serious clinical problems. Physicians should familiarize themselves with the details of its use before prescribing. Ismelin is contraindicated in patients with a pheochromocytoma for two reasons. Since Ismelin initially causes the release of norepinephrine, it may cause a release of the hormone from the tumor, causing a precipitous blood pressure rise. The effect of norepinephrine is augmented by prior treatment with Ismelin, so the release of the hormone by the tumor in a treated patient would have an adverse effect.

**Dosage: Ambulatory Patients**—Individualization of dosage is essential for optimal results. Blood pressure should be taken in both the supine and the standing position at every visit and increases in dosage made only if there has been no decrease in standing blood pressure from the previous levels. Average daily dose is 25 to 50 mg. A single daily dose is generally most convenient.

Dosage Chart for Initiating Ismelin in Ambulatory Patients	
VISITS AT INTERVALS OF 5 TO 7 DAYS	DAILY DOSE
Visit No. 1 (Start with 10-mg. tablets)	10 mg.
Visit No. 2	20 mg.
Visit No. 3 (Patient can be changed to 25-mg. tablets whenever convenient)	30 mg. (three 10-mg. tablets.) or 37½ mg. (one and one-half 25-mg. tablets.)
Visit No. 4	50 mg.
At Visit No. 5, and subsequent visits, the dosage may be increased by 12.5 mg. or 25 mg. if necessary.	

The dosage should be reduced in any one of the following three situations:

1. *Normal supine pressure.* Since Ismelin may have a cumulative effect, it is both desirable and necessary to use the lowest effective dosage.
2. *Excessive orthostatic reduction.*
3. *Severe diarrhea.* While some increase in bowel movements can be easily controlled, severe diarrhea is a sign of overdosage.

**Side effects:** Patients may develop postural hypotension. While symptoms can be minimized by careful dosage adjustment, some patients will experience lightheadedness and dizziness. In patients with severe symptoms, Ismelin should be withheld and should be resumed at lower doses when all symptoms have cleared.

Unlike ganglionic blockers, Ismelin does not cause *impotentia erigendi*. Ejaculation, however, is sometimes completely inhibited.

Diarrhea has been bothersome in some instances; it is frequently controlled with lower doses or with Antrenyl, 5 mg. t.i.d. Other side effects reported in a few patients: mild edema, nasal congestion, fatigue and weakness.

For more complete information on precautions, dosage, and side effects, write to Medical Service Division, CIBA, Summit, N. J.

Supplied: Tablets, 10 mg. (yellow, scored) and 25 mg. (white, scored).

**References:** 1. Page, I. H., and Dustan, H. P.: J.A.M.A. 170:1265 (July 11) 1959. 2. Frohlich, E. D., and Freis, E. D.: M. Ann. District of Columbia 28:419 (Aug.) 1959. 3. Richardson, D. W., and Wiso, E. M.: Virginia M. Month. 66:377 (July) 1959. 4. Brest, A. N., and Moyer, J. H.: J.A.M.A. 172:1041 (March 5) 1960. 5. Page, I. H.: Postgrad. Med. 27:448 (April) 1960. 6. Kirkendall, W. M., Fitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Paper presented at A Symposium on Guanethidine (Ismelin), The University of Tennessee College of Medicine, Memphis, Tenn., April 22, 1960. 7. Leishman, A. W. D., Matthews, H. L., and Smith, A. J.: Lancet 2:1044 (Dec. 12) 1959. Additional references: 8. Brest, A. N., Duarte, C., Glantz, G., and Moyer, J. H.: Current Therap. Res. 2:17 (Jan.) 1960. 9. Maxwell, R. A., Mull, R. F., and Plummer, A. J.: Experimentia 15:267 (July 15) 1959. 10. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. L.: J. Pharmacol. & Exper. Therap. 128:22 (Jan.) 1960. 11. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. L.: Pharmacologist 1:86 (Fall) 1959. 12. Sheppard, H., and Zimmerman, J.: Pharmacologist 1:69 (Fall) 1959.

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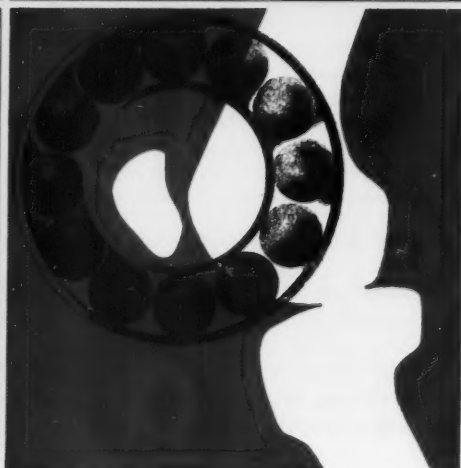
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WHEN PAINFUL MUSCLES RELAX, INFLAMED JOINTS NEED LESS STEROID



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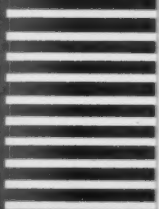
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**makes dry skin feel soft and smooth immediately**

Alpha-Keri effectively deposits a microfine, lubricant-moisturizing oil film over the entire skin area. This oil film:

- relieves itching which often accompanies chronic dry skin and dermatitic skin
- lubricates dry skin and restores protective action similar to that of skin lipids
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Alpha-Keri is the first and only completely water-dispersible, antipruritic oil combining mineral oil and Kerohydric® (brand of keratin-moisturizing fraction of lanolin) and a nonionic emulsifier.

Supplied in 8 fl. oz. bottles.

**Directions:** Alpha-Keri should always be used with water . . . either added to water or rubbed into wet skin.

**Bath** — Add 2 to 4 capfuls to bathtub of water. Soak for 10 to 20 minutes. **Shower** — Add 4 capfuls to about a pint of warm water and apply with a wet cellulose sponge. Rub gently over entire body. Rinse under shower.

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**weight loss ranged  
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HYDROCHLOROTHIAZIDE

**increased potency—without corresponding increase in side effects**



*Sackner, M. A., Wallack, A. A. and Bellet, S.: Am. J. M. Sc. 237:575, (May) 1959.*



“The severity of the congestive heart failure . . . was as follows: Class IV (9 patients), Class III (5 patients), and Class II (1 patient).” . . . “Weight loss ranged from 4 to 45 pounds over a period of 3 to 17 days with an average of 2.4 pounds a day.”

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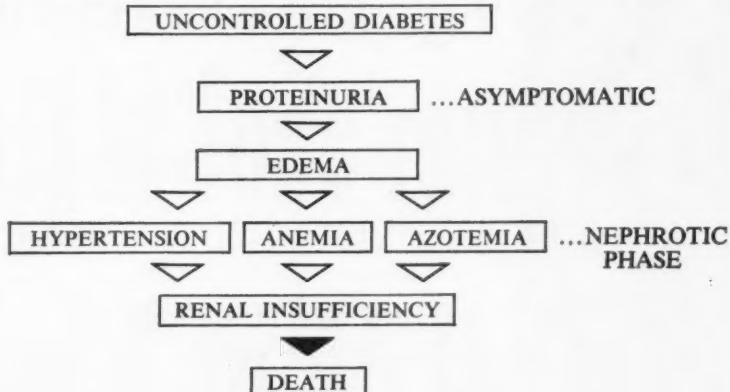
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Source: Whitehouse, F. W.: Postgrad. Med. 24:54, 1958.

### NATURAL HISTORY OF DIABETIC NEPHROPATHY



Adapted from Whitehouse, F. W.: *op. cit.*

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## INCREASED LIFE EXPECTANCY FOR HYPERTENSIVES

"Life expectancy seems to be the one criterion that is most reliable and least questioned as a method of evaluating treatment for patients with elevated blood pressure."<sup>1</sup> "It is evident that effective therapy of hypertension will prolong the life of the patient by preventing the dreaded complications of this disease in the brain, the heart and the kidneys." "There is no doubt of the prolongation of life in group 3 and 4 (Keith-Wagener-Barker) by adequate antihypertensive treatment. Some authorities report a 50 per cent, five year survival ratio for treated patients with malignant hypertension as against a 1 per cent survival ratio for untreated patients."<sup>2</sup>

Evaluation based on life expectancy is extremely difficult because of the peril of maintaining an untreated control group.<sup>1</sup> The doctor, however, can evaluate the symptoms related to the elevated blood pressure. . . . We know that retinopathy may improve, the heart may be reduced in size, the electrocardiogram may improve and in favorable cases the blood urea nitrogen level may fall.<sup>2</sup> These are reasonably objective criteria on which to base one's evaluation of treatment.<sup>1</sup>

On the succeeding page is evidence that Unitensin included in any therapeutic regimen may improve the results in hypertension as measured by a regression of objective clinical changes in a substantial proportion of the patients treated.

1. Currans, J. H.: *New England J. Med.* 261:1062, 1959.
2. Waldman, S. and Pelnor, L.: *Am. Pract. & Digest. Treat.* 10:1139, 1959.
3. Cohen, B. M.: paper presented at A.M.A. Convention, June, 1958.
4. Cohen, B. M.: paper presented at Indiana Acad. G. P., March, 1959.
5. Cohen, B. M.: *Am. J. Cardiology* 1:748, 1958.
6. Kirkendall, W. J.: *J. Iowa M. Soc.* 47:300, 1957.
7. Cherny, W. B., *et al.*: *Obst. & Gynec.* 9:515, 1957.
8. Raber, P. A.: *Illinois M. J.* 108:171, 1955.
9. McCall, M. L., *et al.*: *Obst. & Gynec.* 6:297, 1955.
10. Finnerty, F. A.: *Am. J. Med.* 17:629, 1954.

Unlike diuretics or ganglionic blocking agents, Unitensen lowers blood pressure through widespread vasorelaxation. Normal vasomotor responses are not altered, and there is no venous pooling with resulting postural hypotension.<sup>3-5</sup> Through alleviation of cerebral vasospasm, Unitensen promotes cerebral blood flow and oxygen utilization.<sup>6-9</sup> Furthermore, Unitensen increases cardiac efficiency, improves renal function and tends to arrest the progress of vascular damage.<sup>3,4,10</sup>

### Progress of Objective and Subjective Symptoms in Grades III and IV Hypertension Following Treatment with Unitensen and Unitensen-R

Observations in Patients\* Treated up to 2 Years

Observations in Patients\* Treated up to 3½ Years

## The Course of Subjective Symptoms

Symptom	Number**	Improved	% Improved
Headache	27	21	77.7
Palpitation	20	13	65.0
Angina	15	9	60.0
Dyspnea	17	8	47.0

Number**	Improved	% Improved
43	38	88.0
29	19	65.5
21	16	76.0
27	14	51.0

## Objective Changes Following Treatment

Finding	Number**	Improved	% Improved
Funduscopy Changes	41	24	58.5
Enlarged Heart	20	13	65.0
Abnormal ECG	37	10	27.0
Proteinuria	31	12	38.7
Nitrogen Retention	17	6	35.2

Number**	Improved	% Improved
59	38	66.0
35	23	65.7
45	25	55.5
43	27	62.7
28	10	35.7

Left hand charts from Clinical Exhibit "The Ambulatory Patient with Hypertension" presented AMA Convention, San Francisco, June 22-27, 1958, by B. M. Cohen, M.D.

Right hand charts include patients previously reported who had been continuously maintained on Unitensen and Unitensen-R, plus additional patients later added to the study. From Clinical Exhibit "The Office Diagnosis and Treatment of the Patient with Hypertension" presented American Academy of General Practice, Indianapolis, March 18-19, 1959, by B. M. Cohen, M.D.

\*All patients in this study were initially classified as Smithwick Grades III and IV.

\*\*Expressed as the number of patients exhibiting the symptom recorded.

## UNITENSEN®

Each tablet contains: Cryptenamine (tannates) 2.0 mg.

## UNITENSEN-PHEN®

Each tablet contains: Cryptenamine (tannates) 1.0 mg., Phenobarbital 15 mg.

## UNITENSEN-R®

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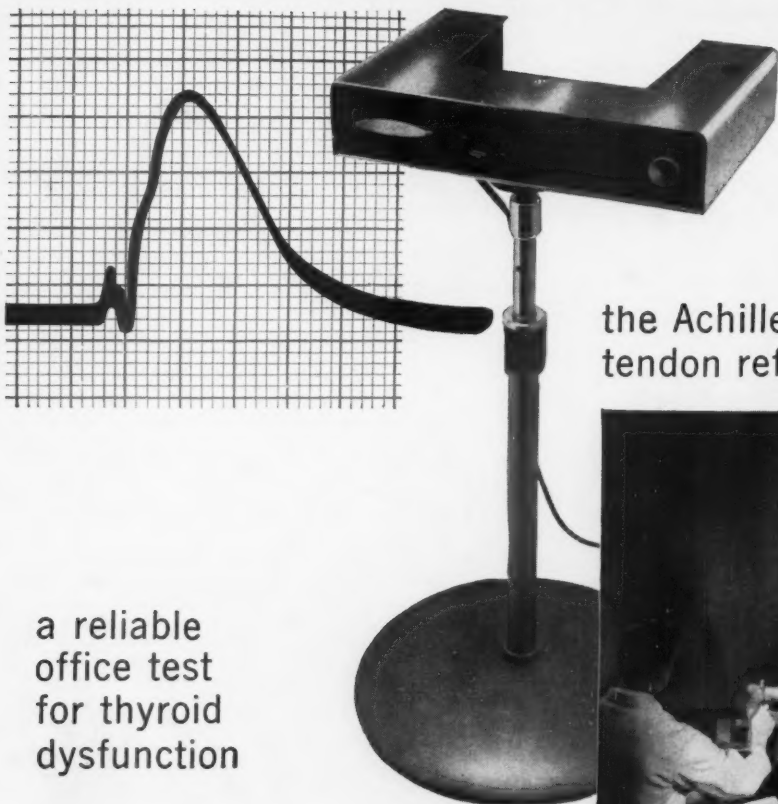
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for the relief of pain and muscle tension

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for thyroid  
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The importance of the relationship between activity of the thyroid gland and the duration of the Achilles tendon reflex response is supported by an increasing number of clinical studies.\*

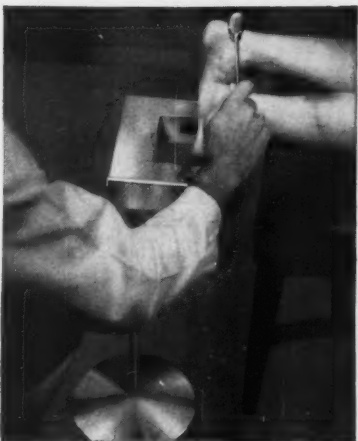
Burdick's new FM-1 PhotoMotoGraph now provides a simplified method for recording this reflex action. The FM-1 utilizes a photoelectric technic to measure displacement of the foot. A standard electrocardiograph, preferably one that will record at a 50 mm per second paper speed to facilitate measurement, gives a permanent tracing of foot movement.

As a diagnostic record for future reference, the Achilles tendon reflex test is valuable. In this respect it should be as much a part of the complete physical examination as the electrocardiogram.

See the FM-1 in action! Your local Burdick dealer will be happy to demonstrate it at your convenience.

\*Abstracts furnished on request.

the Achilles  
tendon reflex



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## specific treatment for arthritic joints

*intra-articular/intrasynovial/intrabursal instillation*

□ **good to excellent response in a vast majority of patients**—"Low doses...provided rapid and effective relief...in almost all of the 157 patients treated..."<sup>1</sup> "...appeared to be superior as an intra-articular injectable substance to anything hitherto available."<sup>2</sup>

□ **provides sustained, long lasting benefits**—In 28 out of 34 patients, "...complete relief was provided by a single injection...the relief lasting for an average of more than 2.5 months."<sup>2</sup>

□ **rapid relief of pain, swelling, and improved range of motion**—"Pain was relieved in 3 or 4 days, or less..."<sup>3</sup> "...marked improvement in range of motion occurred in all of these patients."<sup>3</sup> "...more potent, milligram for milligram, than other injectable corticosteroids."<sup>4</sup>

□ **undesirable side reactions outstandingly rare**—"...appears to be a safe, potent, and effective preparation..."<sup>5</sup> "...tolerated as well as or better than hydrocortisone or prednisolone."<sup>6</sup>

**Dosage:** usual doses—2.5 to 5.0 mg. for smaller joints; 5.0 to 15.0 mg. for larger joints. **Side Effects:** outstandingly rare; although systemic effects do not ordinarily occur with Kenalog Parenteral when the proper techniques and dosages are used, careful clinical supervision is advisable for all patients receiving steroid therapy. **Contraindications:** infections in or near joints—e.g., gonococcal or tuberculous arthritis. **Supply:** a sterile aqueous suspension in 5 cc. vials, each cc. providing 10 mg. triamcinolone acetate. **References:** 1. Sperling, I. L.: Clinical Research Notes vol. 3, No. 1 (Jan.) 1960. 2. Steinberg, C. L.: op. cit. 3. Urist, M. R.: op. cit. 4. Meltzer, L. E.: op. cit. 5. Schwartz, S.: op. cit. 6. Felts, W. R.: op. cit.

Among 363 patients treated with Kenalog Parenteral, 315 (86.7%) obtained complete relief or were markedly improved.<sup>1-4</sup>

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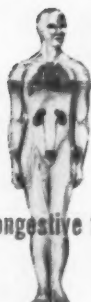
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in congestive failure

"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., 59:1769, (May 1) 1959.



in hypertension

"... our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.



in premenstrual edema

"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., 169:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg. tablets DIURIL once or twice a day. Hypertension—One 250 mg. tablet DIURIL twice a day to one 500 mg. tablet DIURIL three times a day.

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*than for all other diuretic-antihypertensives combined!*



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"One hundred patients were treated with oral chlorothiazide." "In the presence of clinically detectable edema, the agent was universally effective." "Chlorothiazide is at present the most effective oral diuretic in pregnancy." Landesman, R., Ollstein, R. N. and Quinton, E. J.: N. Y. State J. Med., 59:66, (Jan. 1) 1959.



in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.



in renal edema

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



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**DOSAGE:** see PDR for dosage, etc.

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1. Bellet, S.; Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.



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**INJECTABLE QUINAGLUTE**

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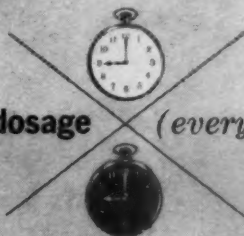
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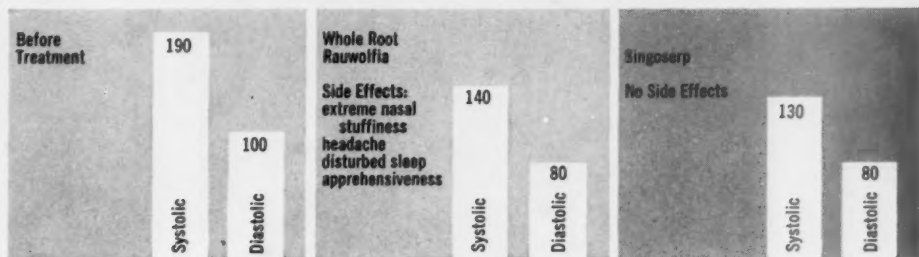
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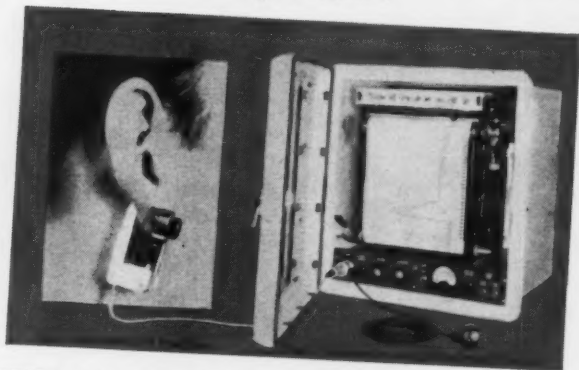
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Records changes of concentration of a dye injected at selected sites in the venous circulation. By its use, cardiac output can be determined and intracardiac shunts can be detected and located. It is also finding in-

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PRIMARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY  
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## **"Thiosulfil" Forte**

See over for therapy in difficult patients ►

**HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION:** Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

### PROOF OF EFFECTIVENESS

In acutely infected patients: Results of seven years' clinical experience:<sup>1</sup> Bourque's report covers 3,057 patients treated with "Thiosulfil" for upper and lower urinary tract infections. The causative organisms were *E. Coli*, *Pseudomonas*, *Klebsiella*, *Enterococcus*, *Staphylococcus*, *Alcaligenes fecalis*, and *Proteus*.

The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:<sup>2</sup> "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections:<sup>3</sup> "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . ."

"'Thiosulfil' was ineffective in only 7 per cent . . ." dosage: 2 Gm./day

### RECORD OF SAFETY

Only these few side effects have been reported with "Thiosulfil." Out of 52 paraplegic cases . . . only one instance of dermatitis.<sup>3</sup> Out of 50 cases . . . mild reactions consisted of slight gastric distress (1); flatulence (3); rash (1); pruritus (1); transient crystalluria (2).<sup>4</sup> Out of 38 cases of chronic infection . . . mild reactions of: stomach and eye discomforts (1); dizziness (1); slight diarrhea (1).<sup>2</sup> Out of 100 cases . . . one reaction—nausea.<sup>5</sup> Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.<sup>1</sup> Out of 300 cases . . . one reaction (appetite loss and lassitude).<sup>6</sup> NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

**The Sulfa Compound Used Successfully Without Interruption for: one month;<sup>3,4</sup> more than 6 weeks;<sup>2</sup> 90 days;<sup>5</sup> 18 months;<sup>3</sup> 5 to 6 years.<sup>7</sup>**

### DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day <sup>1</sup>
2 weeks to 3 months	2 Gm./day <sup>3,4</sup>
3 months or longer	0.5 Gm./day <sup>7</sup>

**Suggested Range of Dosage:** 1 or 2 tablets three or four times daily. **Note:** The usual precautions exercised with sulfonamides should be observed. **Supplied:** No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

**References—**1. Bourque, J.-P., and Gauthier, G.E.: Seven years' experience with sulfamethizole, to be published. 2. Barnes, R. W.: *J. Urol.* 71:655 (May) 1954. 3. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: *Rocky Mountain M. J.* 56:66 (Mar.) 1953. 4. Bourque, J.-P., and Joyal, J.: *Canad. M.A.J.* 68:337 (Apr.) 1953. 5. Hughes, J., Coppridge, W. M., and Roberts, L. C.: *South. M. J.* 47:1082 (Nov.) 1954. 6. Goodhope, C. D.: *J. Urol.* 72:552 (Sept.) 1954. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: *North Carolina M. J.* 17:320 (July) 1956.

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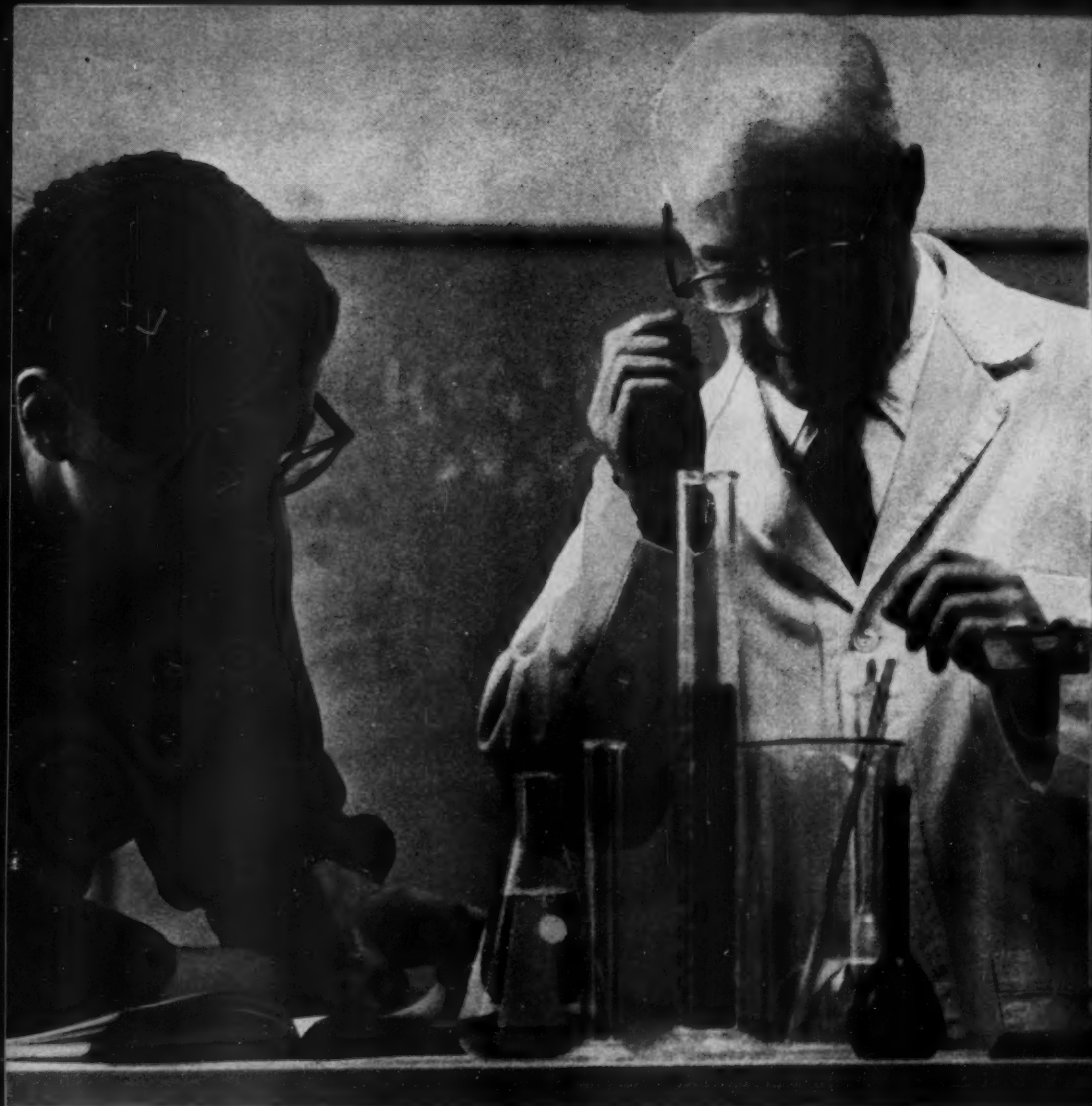
1. Beil, A.: Management of Constipation in the Puerperium. To be published.



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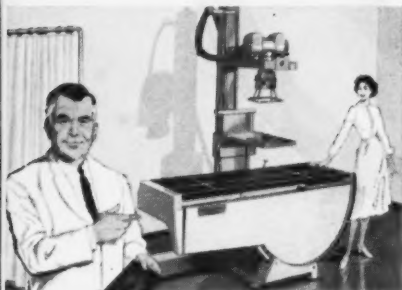


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\*Knudsen, E. T., and Rolinson, G. N.: *Lancet* 2:1105 (Dec. 19) 1959.

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**REFERENCES:** 1. Lorber, S. H., and Shay, H.: *Gastroenterology* 28:274, 1955. 2. Hock, C. W.: *J. M. A. Georgia* 40:22, 1951. 3. Chamberlin, D. T.: *Gastroenterology* 17:224, 1955. 4. Steves, M. F.: *Ohio State M. J.* 48:615, 1952. 5. Derome, L.: *Canad. M. A. J.* 69:532, 1953. 6. Pakula, S. F.: *Postgrad. Med.* 11:123, 1952. 7. Guerrero, R. M., Cancio, R., and Songco, R.: *Phil. J. Pediat.* 2:30, 1953. 8. Hock, C. W.: *J. M. A. Georgia* 49:124, 1954. 9. Hufford, A. R.: *Am. J. Digest. Dis.* 19:257, 1952. 10. Brown, D. W., and Guilbert, G. D.: *Am. J. Ophth.* 36:1785, 1953. 11. Cholat, M., Goodstein, S., Berens, C., and Cinotti, A.: *J. A.M.A.* 166:1276, 1958. 12. Brown, B. B., Thompson, C. R., Klahm, G. R., and Werner, H. W.: *J. Am. Pharm. A. (Sc. Edit.)* 39:305, 1950. 13. Hufford, A. R.: *J. Michigan M. Soc.* 49:1308, 1950. 14. McHardy, G. G., Browne, D. C., Marek, F. H., McHardy, R., and Ward, S.: *J.A.M.A.* 147:1620, 1951. 15. Esses, E., Magee, D. F., and Ivy, A. C.: *Gastroenterology* 21:574, 1952. 16. Northrup, D. W., Stickney, J. C., and Van Liere, E. J.: *Am. J. Physiol.* 171:513, 1952.

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17. Lorber, S. H., and Shay, H.: *Fed. Proc.* 12:90, 1953. 18. Johnston, R. L.: *J. Indiana M. A.* 46:869, 1953. 19. Marien, E., Webster, D. R., and Tidmarsh, C. J.: *Gastroenterology* 24:280, 1953. 20. Hardin, J. H., Levy, J. S., and Seager, L.: *South. M. J.* 47:1190, 1954. 21. Seisenger, M. H., Eisenbud, M., and Almy, T. P.: *Gastroenterology* 27:829, 1954. 22. Weiss, S.: *Am. J. Gastroenterology* 23:69 (Editorial) 1955. 23. Illingworth, R. S.: *Lancet* 2:1119, 1959. 24. McHardy, G. G., and Browne, D. C.: *South. M. J.* 45:1189, 1952. 25. Miller, B. N.: *J. South Carolina, M. A.* 48:1, 1952.



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TOTAL	103	79	16	8

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1. Billow, B.W., et al.: Southwestern Med. 41:286, 1960.
2. Teitel, L. H., et al.: Indust. Med. 29:150, (April) 1960.
3. Taub, S. J.: Paper presented before the Annual Meeting, Pi Lambda Kappa Medical Fraternity, Miami, Florida (March) 1960.
4. Clinical Reports to the Medical Dept., Armour Pharmaceutical Co., 1959.

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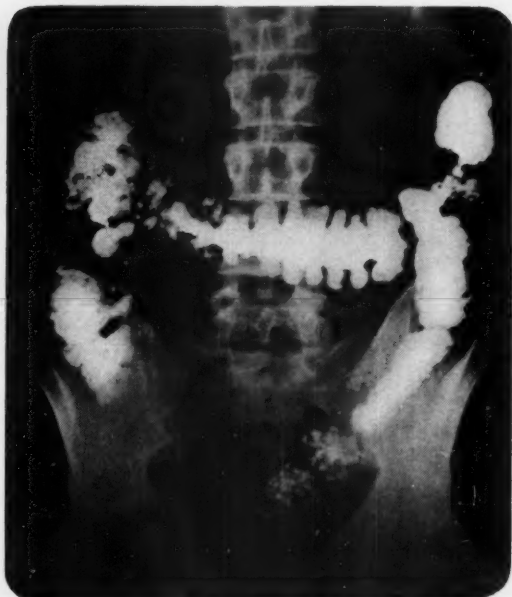
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		84.7%		15.3%
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\*Includes irritable bowel syndrome, regional enteritis, diverticulitis, ulcerative colitis, postantibiotic enteritis, malabsorption syndrome, radiation proctitis, surgically short-circuited intestinal states. \*\*Includes nonspecific gastroenteritis, enteritis, enterocolitis.

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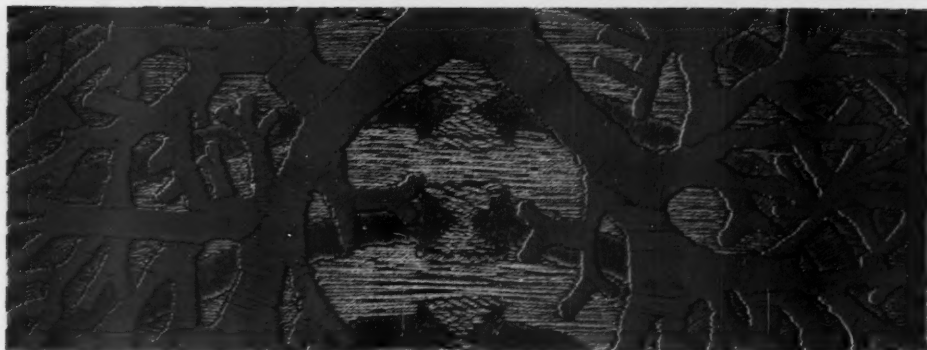
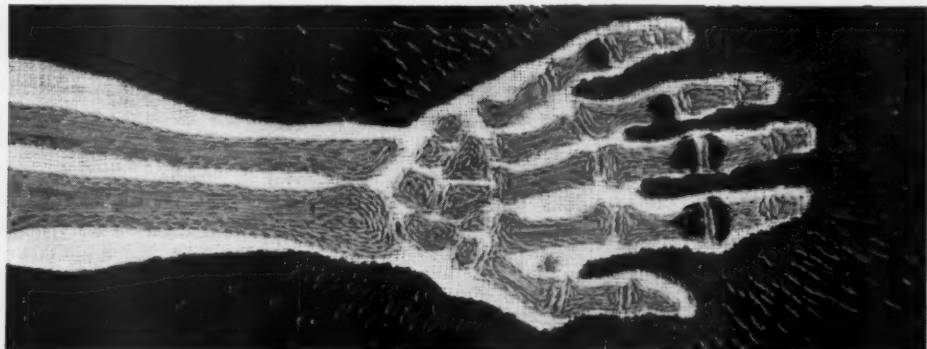
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**REFERENCES:** 1. Winkelstein, A.: *Am. J. Digestive Dis.*: In press. 2. Berkowitz, D.: Personal communication. 3. Hock, C. W.: *Med. Times* 88:320 (March) 1960. 4. Lind, H. E.: Personal communication. 5. Seneca, H.: In press. 6. Riese, J. A.: Personal communication. 7. Gilbert, A. S.; Schwartz, I. R., and Matzner, M. J.: Submitted for publication. 8. Personal communications to Medical Department, White Laboratories, Inc. *Additional bibliography:* 9. Pimparker, B. D.; Paustian, F. F.; Roth, J. L. A., and Bockus, H. L.: To be published. 10. Texter, E. C.: Personal communication. 11. Clinical Reports to Medical Department, White Laboratories, Inc. 12. Grossman, A. J.; Batterman, R. C., and Leifer, P.: *J. Am. Geriat. Soc.* 5:187 (Feb.) 1957. 13. McHardy, G.; Browne, D.; McHardy, R.; Bodet, C., and Ward, S.: *Am. J. Gastroenterol.* 24:601 (Dec.) 1955. 14. Shay, H.: Personal communication. 15. Hirsh, H.: Personal communication. 16. Bercovitz, Z. T.: *J. Am. Geriat. Soc.* 5:940 (Nov.) 1957.



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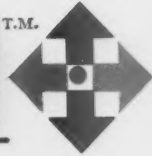
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**supplied:** Scored tablets, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. tsp., 16 oz. bottles.

**references:** (1) Clinical Research Division, Mead Johnson & Company. (2) Howell, C. M., Jr.: Evaluation of Methdilazine as an Antipruritic Agent, North Carolina M. J. 21 (May) 1960 (in press). (3) Wahner, H. W., and Peters, C. A.: An Evaluation of Some Newer Antihistaminic Drugs Against Pollinosis, Proc. Staff Meet. Mayo Clin. 35:161-169 (March 30) 1960.



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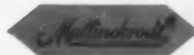
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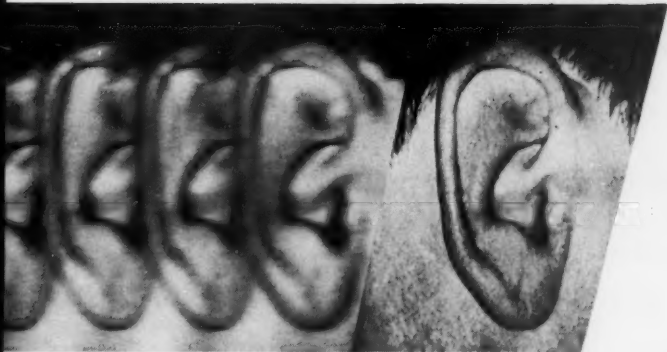
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(triparanol)

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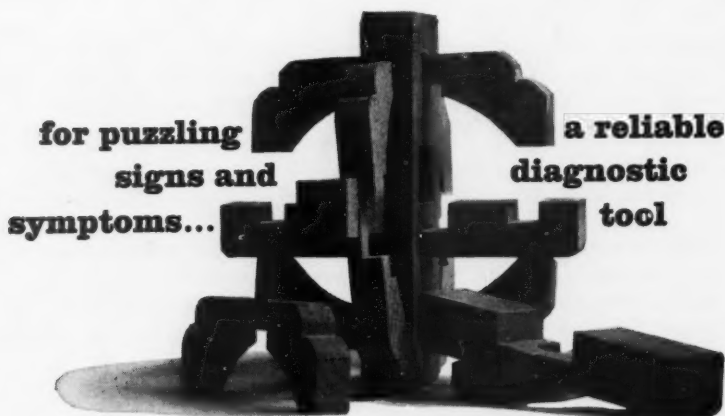
*References:* 1. Hollander, W., and Chobanian, A. V.: *Boston M. Quart.* 10:37 (June) 1959. 2. Oaks, W., and Lisan, P.: *Fed. Proc.* 18:428 (Mar.) 1959. 3. Oaks, W. W., *et al.*: *A. M. A. Arch. Int. Med.* 104:527 (Oct.) 1959. 4. Lisan, P.: *Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis.* 2:(Suppl.) 618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., *et al.*: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: *J.A.M.A.* 173:884 (June 25) 1960.



THE WM. S. MERRELL COMPANY  
Cincinnati 15, Ohio • St. Thomas, Ontario

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TRADEMARK: "MER/29"



When signs and symptoms refuse to fall into place, the C.R.P.A. test accurately indicates inflammatory and necrotic diseases. A simple office procedure taking less than two minutes to set up and perform, the C.R.P.A. test can be used *prior to other tests* to determine the necessity for an erythrocyte sedimentation rate or SGO-T level.

Unlike the ESR or SGO-T level, a C.R.P.A. test demonstrates no variability in normal values. Any positive reaction may be considered abnormal.<sup>1,2</sup> It is influenced only by the C-reactive protein in the patient's blood and gives fewer false positives than other indexes of inflammation.<sup>1,2</sup>

The C.R.P.A. test is a reliable indicator of acute myocardial infarction,<sup>1-9</sup> acute rheumatic fever,<sup>10-12</sup> active widespread malignant disease,<sup>1,6,7,12,13</sup> and bacterial infections.<sup>1,5,7,14</sup>

# C·R·P·A<sup>®</sup> test

**fits into the basic diagnostic routine**

The sensitiveness of the C.R.P.A. test makes it helpful in differential diagnoses.<sup>4,5</sup> It may be used to deny or confirm ESR and SGO-T readings. It can also be used to mark the progress of the disease and measure the effectiveness of therapy.<sup>1,4,15</sup>



**References:** 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 3. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 4. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:90, 1957. 5. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 6. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 7. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

Complete literature and bibliography available on request.



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# **CHOLEDYL**

## **CANDIDATE**

**STRANGLED WITH AIR**

*in respiratory distress*

# **CHOLEDYL®**

brand of oxtriphylline

*better breathing . . . decreases wheezing in chronic bronchitis, chronic asthma and emphysema*

Choledyl, the choline salt of theophylline, produces up to 75% higher theophylline blood levels than does oral aminophylline, without gastric upset. The superior specific bronchodilator, Choledyl is basic for prophylaxis or treatment of dyspnea . . . has no sedative or sympathomimetic effects . . . reduces incidence and severity of acute attacks . . . decreases need for secondary medication . . . retains effectiveness during long-term administration. *Usual dose: 200 mg. q. i. d. Supplied as 200 mg. tablets (yellow), bottles of 100.*



MORRIS PLAINS, N.J.

8703

## after milk and rest, why Donnalate?

Once you've prescribed milk and rest for a peptic ulcer patient, Donnalate may be the best means for fulfilling his therapeutic regimen. This is because Donnalate combines several recognized agents which effectively complement each other and help promote your basic plan for therapy. A single tablet also simplifies medicine-taking.

**in Donnalate:** Dihydroxyaluminum aminoacetate affords more consistent neutralization than can diet alone. • Phenobarbital improves the possibility of your patient's resting as you told him to. • Belladonna alkaloids reduce GI spasm and gastric secretion. And by decreasing gastric peristalsis, they enable the antacid to remain in the stomach longer.

Each Donnalate tablet equals one Robalate® tablet plus one-half Donnatal® tablet: Dihydroxyaluminum aminoacetate, N. F., 0.5 Gm.; Phenobarbital ( $\frac{1}{2}$  gr.), 8.1 mg.; Hyoscyamine sulfate, 0.0519 mg.; Atropine sulfate, 0.0097 mg.; Hyoscine hydrobromide, 0.0033 mg.

# Donnalate®

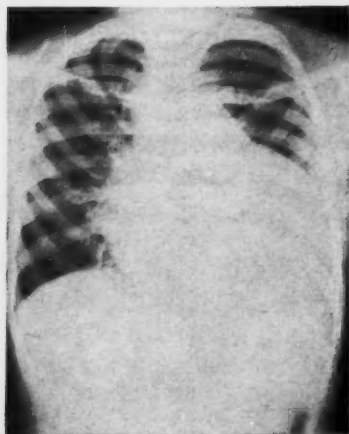
**A. H. Robins Co. INC.**  
RICHMOND 20, VIRGINIA



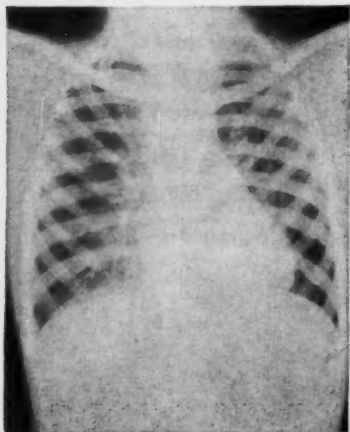
THE UPJOHN COMPANY  
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Upjohn

## Cardiac damage reduced in acute rheumatic fever



Pericarditis with pericardial effusion; roentgenogram before therapy.



Dramatic reduction in heart size after pericardial tap of only 150 cc. and 6 days of Medrol therapy.

X-rays courtesy of Lorin E. Ainger, M.D.

In 243 patients hospitalized for acute rheumatic fever, *high-dosage corticotherapy* led to regression or disappearance of significant murmurs at least twice as often as did management with salicylate, small doses of steroid, or no medication. *Early initiation of therapy* increased the percentage of patients showing cardiac improvement.<sup>1</sup>

**there is only one  
methylprednisolone,  
and that is**

# Medrol\*

**the corticosteroid  
that hits the disease,  
but spares the patient**



Supplied: As 4 mg. tablets in bottles of 30, 100 and 500; as 2 mg. tablets in bottles of 30 and 100; and as 16 mg. tablets in bottles of 50.

\*TRADEMARK, REG. U. S. PAT. OFF.—  
METHYLPREDNISOLONE, UPJOHN

1. Massell, B. F.: Paper presented at A Symposium on Steroid Therapy, Chicago, Ill., May 15-16, 1959.

**INTRAVENOUS CONTRAST MEDIA  
FOR VIRTUALLY EVERY UROGRAPHIC  
AND ANGIOGRAPHIC NEED...**

# **RENOGRAFIN**

Squibb Diatrizoate Methylglucamine

## **RENOGRAFIN 76%**

for intravenous urography and angiography. Ampuls of 20 cc. and 1 cc. for sensitivity testing. Each cc. contains 760 mg. of diatrizoate methylglucamine.

## **RENOGRAFIN 60%**

for intravenous urography and angiography. Ampuls of 25 cc. and 1 cc. for sensitivity testing. Each cc. contains 600 mg. of diatrizoate methylglucamine.

## **RENOGRAFIN 30%**

for retrograde pyelography. Rubber-capped vials of 50 cc. Each cc. contains 299 mg. of diatrizoate methylglucamine.

## **NEW**

# **RETROGRAFIN**

Squibb Diatrizoate Methylglucamine and Neomycin Sulfate

## **FOR RETROGRADE PYELOGRAPHY WITH ADDED ANTIBACTERIAL PROTECTION...**

Retrogratin provides all the advantages of Renografin 30% and in addition, it contains 2½% neomycin (as sulfate) for widely effective bactericidal action in cases of proved or suspected urinary tract infection. Supplied in 50 cc. vials.

**well tolerated systemically and locally ...**

"In view of the low incidence of reactions, we prefer Renografin to other opaques tested."

DeCarlo, J., and Sod, L.M.: Clinical Report to the Squibb Institute for Medical Research, March, 1956.

**excellent visualization ...**

"... excellent opacification was obtained in a high percentage of the patients..."

Dennis, J.M.: Clinical Report to the Squibb Institute for Medical Research, March, 1956.

**permits rapid completion of the urographic examination ...**

"As little as 5 minutes after the end of the injection, we obtained constant and good visualization of the renal pelvis and calyces."

Babaianz, L., and Wieser, C.: Praxis 34:454 (May 19) 1955.

**SQUIBB**



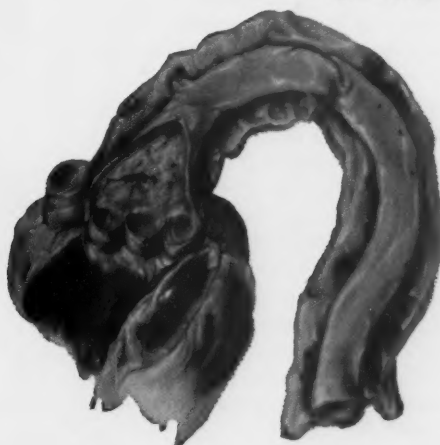
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If the patient can be digitalized and maintained at all, he can be digitalized and maintained with GITALIGIN—and sometimes he can be digitalized and maintained only with

WIDER  
SAFETY  
MARGIN

GITALIGIN<sup>®†</sup>

*"The digitalis preparation of choice..."\**



GITALIGIN provides a maximum degree of control in cardiac therapy by reason of these distinctive clinical features \*\* WIDER SAFETY MARGIN • GREATER THERAPEUTIC RANGE • FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

It's easy to transfer patients to GITALIGIN—WITHOUT INTERRUPTION—0.5 mg. Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.1 mg. digitoxin, and 0.5 mg. digoxin. Supplied: 0.5 mg. scored tablets—in bottles of 30 and 100. \*Batterman, R. C., et al.: *Circulation* 5:201, 1952. \*\*Bibliography available on request.

†White's brand of amorphous gitalin. WHITE LABORATORIES, INC., KENILWORTH, N. J.

White

# safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.<sup>1-3</sup> Figure #1 graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.<sup>3</sup>

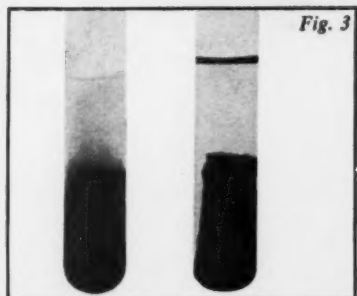
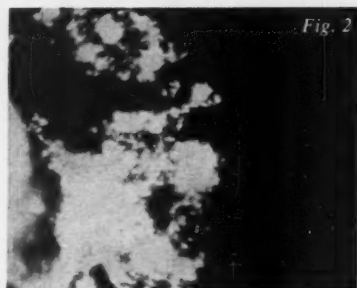
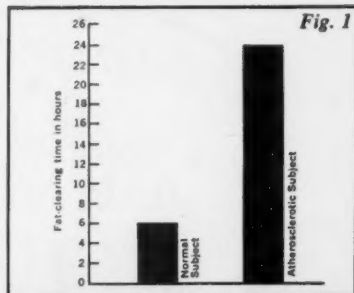
"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in figure #2, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,<sup>4</sup> and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.<sup>5</sup>

In figure #3, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarín', which is heparin in the form of a sublingual tablet, has been demonstrated to clear lipemic serum.<sup>2,6,7</sup> Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarín'.<sup>8</sup>

'Clarín' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

**References:** 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. 45:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. 163:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959. 8. Fuller, H. L.: Circulation 20:699 (Oct.) 1959.



**Indication:** For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

**Dosage:** After each meal, hold one tablet under the tongue until dissolved.

**Supplied:** 'Clarín' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

\*Registered trade mark. Patent applied for.

*Thos. Leeming & Co., Inc.*  
New York 17, N. Y.

# Clarín\*

(sublingual heparin potassium, Leeming)





you get these results in case after case of edema  
and hypertension with **ESIDRIX®**

hospitalized  
patient with  
congestive  
heart failure



5 pounds lost in 4  
days; 4+ pitting  
cleared; hepatic  
congestion and  
râles cleared;  
patient  
ambulatory



office patient  
treated for  
pedal edema  
and persistently  
high diastolic  
pressure



blood pressure  
reduced from  
214/110 to  
180/94 mm. Hg  
within 7 days with  
Esidrix (and  
Singoerp); pitting  
edema cleared



private patient  
with congestive  
heart failure;  
ascites and  
4+ edema  
to the knee



12½ pounds lost  
in 13 days; basilar  
râles and ascites  
no longer present;  
pitting edema  
of legs and  
feet cleared



hospitalized  
patient with  
Laennec's  
cirrhosis



27 pounds lost in  
19 days; abdominal  
swelling and  
pedal edema  
cleared



*Photos used with  
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marked benefits in  
patient after patient with  
edema and hypertension  
plus built-in  
potassium protection

# NEW **ESIDRIX-K**<sup>T.M.</sup>

- ESIDRIX-K provides all the oral diuretic-antihypertensive benefits of Esidrix, plus a generous potassium supplement.
- Three tablets supply 75 mg. Esidrix plus potassium equivalent to a quart of fresh orange juice. ESIDRIX-K is coated to prevent gastric irritation.
- In edema, Esidrix produces marked salt and water excretion with only minimal potassium excretion. With ESIDRIX-K, the built-in supplement further helps eliminate problems due to potassium loss.
- In hypertension, ESIDRIX-K alone or with other antihypertensive drugs significantly reduces blood pressure in many patients.
- ESIDRIX-K may be effective in patients refractory to chlorothiazide.
- Many hypertensive patients can be maintained on only 1 ESIDRIX-K tablet per day.

*Complete information sent on request.*

*Supplied:* Esidrix-K Tablets (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride; bottles of 100. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

ESIDRIX® (hydrochlorothiazide CIBA)

All patients shown at left were treated with Esidrix. **Esidrix-K is especially indicated** for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt restricted diets.



2/2040W9

One-at-Bedtime

TRAL 75 mg.  
GRADUMET

NEW "AUTOMATIC"  
CONTROL OF  
NIGHTTIME  
GASTRIC SECRETION

# TRAL<sup>®</sup> 75<sup>mg.</sup> Gradumet<sup>®</sup>

**Built-in timing actually  
steps up drug release dur-  
ing critical 2-4 a.m. period**

Nighttime gastric secretion hits its peak between 2 and 4 a.m. And that's just when Tral 75 mg. Gradumet, taken at bedtime, is releasing most of its anticholinergic. The patient gets most of the medication when he needs it most . . . in the middle of the night. • Thereafter, Tral 75 mg. Gradumet keeps right on working until the patient awakens the next morning, after a refreshing sleep. And since acidity is controlled the night through, the ulcer has a better chance to heal. • Gradumet's built-in timing is dependable, too . . . never affected by coating thickness, pH or other variables.

• In bottles of 50 and 500.



**. . . and when the problem  
is functional bowel disorder  
specify new Filmtab<sup>®</sup>**

## TRALCYON<sup>™</sup>

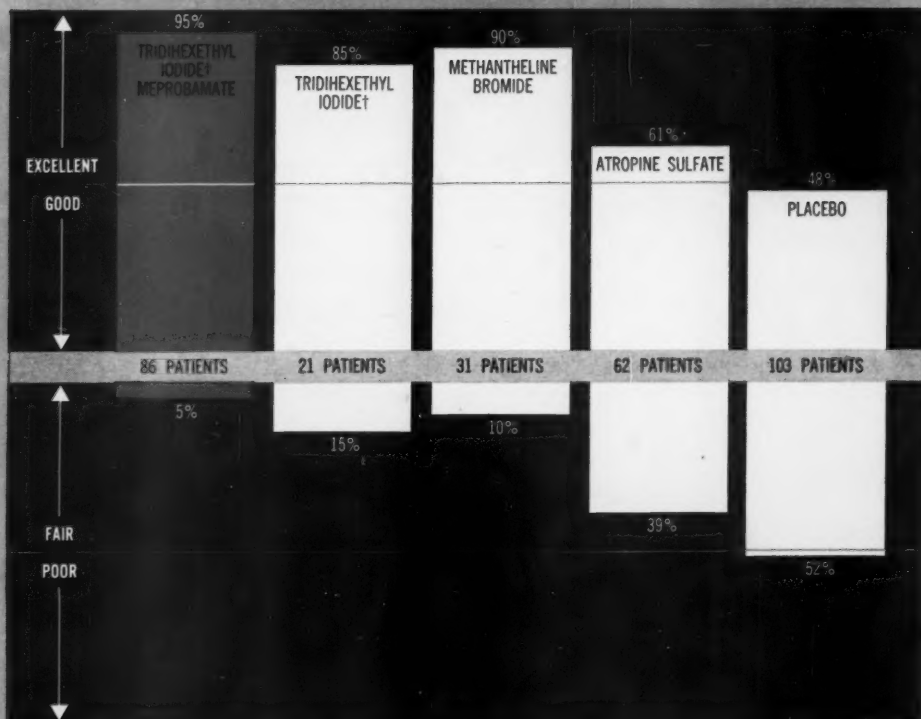
**each Filmtab offers 25 mg.  
Tral plus 300 mg. ectylurea**

© Tral Gradumet—Hexocyclium Methylsulfate in Long-Release Dose Form\*, Abbott. \*Patent applied for. © Filmtab—Film-sealed tablets, Abbott.

000207

# clinically proven efficacy...

in relieving tension... curbing hypermotility and excessive secretion in G. I. disorders



**PATHIBAMATE** combines two highly effective and well-tolerated therapeutic agents:

**Meprobamate**—widely accepted tranquilizer and

**PATHILON** tridihexethyl chloride—anticholinergic noted for its effect on motility and gastrointestinal secretion with few unwanted side effects.

**Contraindications:** glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Two available dosage strengths permit adjusting therapy to the G.I. disorder and degree of associated tension.

Where a minimal meprobamate effect is preferred...

**PATHIBAMATE-200** Tablets: 200 mg. of meprobamate; 25 mg. of **PATHILON**

Where a full meprobamate effect is preferred...

**PATHIBAMATE-400** Tablets: 400 mg. of meprobamate; 25 mg. of **PATHILON**

**Dosage:** Average oral adult dose is 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

# Pathibamate® 400/200

meprobamate with **PATHILON**® tridihexethyl chloride Lederle



# ...clinically proven safety

The efficacy of **PATHIBAMATE** has been confirmed clinically in duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, and gastric hypermotility.

Pictured are the results obtained with the **PATHILON** (tridihexethyl iodide)–meprobamate combination† in a double-blind study of 303 ulcer patients, extending over a period of 36 months.\* They clearly demonstrate the efficacy of **PATHIBAMATE** in controlling the symptoms.

SIDE EFFECTS	TRIDIHETHYL IODIDE† MEPROBAMATE	TRIDIHETHYL IODIDE†	METHANTHILINE BROMIDE	ATROPINE SULFATE	PLACEBO
DRY MOUTH	1%	5%	72%	46%	5%
STOMATITIS	1%	0%	28%	14%	0%
VISUAL DISTURBANCES	0%	0%	50%	34%	1%
URINARY RETENTION	0%	0%	18%	11%	1%
DROWSINESS	20%	0%	0%	0%	0%
COMPLICATIONS OR SURGERY					
HEMORRHAGE	0%	9%	3%	9%	10%
PERFORATION	0%	0%	0%	6%	0%
OPERATION	0%	5%	5%	14%	2%
RECURRENCES					
NONE	20%	23%	25%	17%	26%
FEWER AND Milder	67%	62%	52%	37%	24%
SAME OR MORE	5%	15%	23%	46%	50%

\*Atwater, J. S., and Carson, J. M.: Therapeutic Principles in Management of Peptic Ulcer. *Am. J. Digest. Dis.* 4:1055 (Dec.) 1959.

†PATHILON is now supplied as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could distort the results of certain thyroid function tests.



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

## control the tension — treat the trauma

When summertime  
chores bring on  
**LOW BACK PAIN**

**Trancopal®**

Brand of chlormezanone

relaxes skeletal  
muscle spasm—  
ends disability.

When any of a host of summer activities brings on low back pain associated with skeletal muscle spasm, your patient need not be disabled or even uncomfortable. The spasm can be relaxed with Trancopal, and relief of pain and disability will follow promptly.

Lichtman<sup>1,2</sup> used Trancopal to treat patients with low back pain, stiff neck, bursitis, rheumatoid arthritis, osteoarthritis, trauma, and postoperative muscle spasm. He noted that Trancopal produced satisfactory relief in 817 of 879 patients (excellent results in 268, good in 448 and fair in 101).

Gruenberg<sup>3</sup> prescribed Trancopal for 70 patients with low back pain and observed that it brought marked improvement to all. "In addition to relieving spasm and pain, with subsequent improvement in movement and function, Trancopal reduced restlessness and irritability in a number of patients."<sup>3</sup> In another series, Kearney<sup>4</sup> reported that Trancopal produced relief in 181 of 193 patients suffering from low back pain and other forms of musculoskeletal spasm.

Trancopal enables the anxious patient to work or play. According to Gruenberg, "In addition to relieving muscle spasm in a variety of musculoskeletal and neurologic conditions, Trancopal also exerts a marked tranquilizing action in anxiety and tension states."<sup>3</sup> Kearney<sup>4</sup> found "... that Trancopal is the most effective oral skeletal muscle relaxant and mild tranquilizer currently available."

Side effects are rare and mild. "Trancopal is exceptionally safe for clinical use."<sup>3</sup> In the 70 patients with low back pain treated by Gruenberg,<sup>3</sup> the only side effect noted was mild nausea which occurred in 2 patients. In Lichtman's group, "No patient discontinued chlormethazanone [Trancopal] because of intolerance."<sup>1</sup>

**How Supplied:** Trancopal Caplets®

200 mg. (green colored, scored), bottles of 100  
100 mg. (peach colored, scored), bottles of 100.

**Dosage:** Adults, 200 or 100 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

**References:** 1. Lichtman, A. L.: *Kentucky Acad. Gen. Pract.* 7, 4:28, Oct. 1958. 2. Lichtman, A. L.: Scientific Exhibit, Internat. Coll. Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 3. Gruenberg, Friedrich: *Current Therap. Res.* 2:1, Jan., 1960. 4. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960.

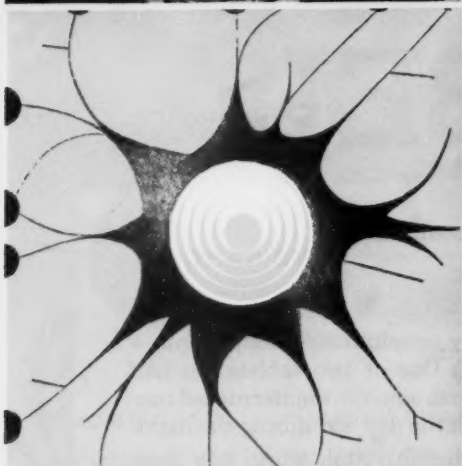
**Winthrop** LABORATORIES  
New York 18, N.Y.

TRANCOPAL (BRAND OF CHLORMETHAZANONE) AND CAPLETS®, TRADEMARKS REG. U. S. PAT. OFF.  
1550M



**whenever depression  
complicates the picture**

**Tofrānil<sup>®</sup>**  
brand of imipramine HCl



**hastens recovery**

**Geigy**

In many seemingly mild physical disorders an element of depression plays an insidious etiologic or complicating role.

Because of its efficacy as an antidepressant, coupled with its simplicity of usage, Tofrānil is admirably adapted to use in the home or office in these milder "depression-complicated" cases.

It is always wise to recognize that depression may be an underlying factor... that Tofrānil may speed recovery in "hypochondriasis"; in convalescence when recovery is inexplicably prolonged; in chronic illness with dejection; in the menopausal patient whose emotional disturbances resist hormone therapy; and in many other comparable situations in which latent depression may play a part.

Detailed Literature Available on Request

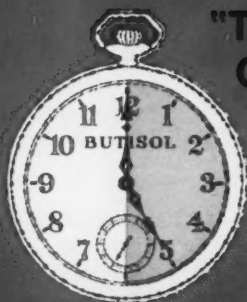
Tofrānil<sup>®</sup>, brand of imipramine hydrochloride, tablets of 25 mg. Ampuls for intramuscular administration, 25 mg. in 2 cc. of solution.

Geigy, Ardsley, New York



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## "TIME-MATCHED" COMPONENTS

for  
smoother  
management  
of smooth  
muscle spasm



# BUTIBEL®

TIME-MATCHED



**ANTISPASMODIC**



**SEDATIVE**

COMBINATION

BUTIBEL combines two essentially synchronous components—belladonna extract and BUTISOL®. One or two tablets one-half hour before meals and at bedtime assures smooth, uninterrupted control of gastrointestinal spasm through the day and during the night.

Similar preparations containing phenobarbital, which has three times the duration of action of belladonna, must either build up a cumulative sedative burden or leave patients for long hours without effective antispasmodic protection.

By contrast, BUTIBEL, with its time-matched components, gives full, continuous antispasmodic *and* sedative action for smooth control of functional gastrointestinal disorders.

**BUTIBEL:** belladonna extract . . . 15 mg. and BUTISOL Sodium® . . . 15 mg.  
butabarbital sodium

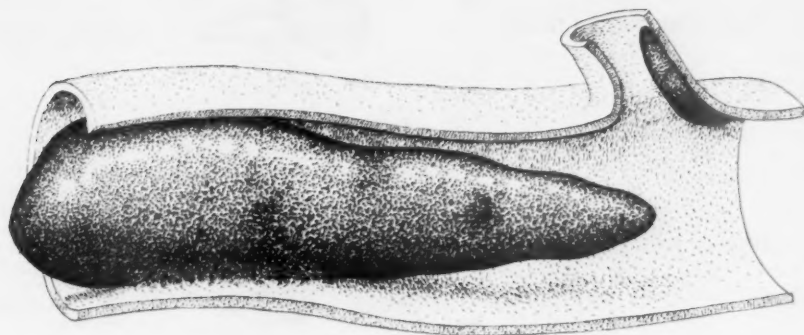
**BUTIBEL** Tablets • Elixir • Prestabs® Butibel R-A (Repeat Action Tablets)

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McNEIL LABORATORIES, INC. Philadelphia 32, Pa.

Announcing...a new agent for lysis of

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**THROMBOLYSIN**, supplemented by anticoagulant therapy, can greatly reduce mortality and morbidity in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.\* Recently formed clots are lysed rapidly, usually in 24 hours.

to lyse thrombi

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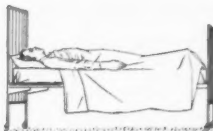

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# THROMBOLYSIN<sup>®</sup>

FIBRINOLYSIN, HUMAN

early use greatly reduces morbidity and mortality in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi

Results of therapy	Bed rest
<p><b>Effect on intravascular thrombi</b></p>	 <p>Clot may form permanent obstruction to blood flow. New clots may form.</p>
<p><b>Effect on pulmonary emboli</b></p>	 <p>Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.</p>
<p><b>Effect on duration of illness and convalescence</b></p>	 <p>Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.</p>
<p><b>Frequency and severity of postphlebotic syndrome</b></p>	 <p>Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.</p>



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**Anticoagulant + Bed rest**

Anticoagulants cannot remove formed clot. However, they help prevent its extension and minimize formation of new clots.



The careful use of anticoagulants reduces the occurrence of pulmonary emboli.



Thromboembolic illness and convalescence are shortened.



The incidence and severity of the postphlebotic syndrome are reduced.

**THROMBOLYSIN + Anticoagulant + Bed rest**

Recently formed intravascular clots are lysed and the formation of new clots is inhibited. Circulation is restored and maintained, with rapid symptomatic relief.



The incidence and severity of pulmonary emboli are greatly reduced since THROMBOLYSIN acts to remove thrombi before they can become emboli.



A striking reduction is observed in the duration of hospital stay, bed rest, and convalescence.



Postphlebotic complications are prevented or greatly minimized.



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*What is THROMBOLYSIN?*

THROMBOLYSIN is Fibrinolysin, Human. It is prepared by activating the profibrinolysin-rich Fraction III — 3 of pooled human plasma with highly-purified streptokinase and then lyophilizing it. THROMBOLYSIN helps restore the natural equilibrium between clot formation and clot lysis, thereby enhancing the ability of the blood to maintain normal flow.

*In What Conditions is it Indicated?*

THROMBOLYSIN is indicated in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.

*\*(NOTE: Successful lysis of thrombi of major cerebral vessels has been reported. However, additional experience is required to define the indications and contraindications of therapy in such patients. THROMBOLYSIN has also been administered to patients with acute myocardial infarction, but the scope of this work is still too limited to permit conclusions about its safety or benefit.)*

*When Should Therapy be Initiated?*

Treatment with THROMBOLYSIN should be started as soon as possible after a thrombus has formed. Blood clots begin to organize shortly after formation and may become encased in a layer of endothelial cells, making them resistant to the action of THROMBOLYSIN. Usually, more rapid lysis can be expected to take place when treatment is initiated within five days after a thrombus has formed; however, in some cases successful lysis has been accomplished when treatment was not initiated for several weeks after thrombus formation.

*Can THROMBOLYSIN be Given to Patients Being Treated with Anticoagulants?*

Yes. Patients who have been on anticoagulant therapy can be expected to improve when THROMBOLYSIN is added to their program of treatment.

*Does THROMBOLYSIN Increase the Incidence of Embolism?*

Clinical studies indicate that it does not. In fact, if any evidence of embolization should appear, it is important to continue THROMBOLYSIN until symptoms have disappeared.

*What is the Dosage?*

The dosage most frequently used by investigators has been 4 vials (200,000 MSD units) per day by intravenous infusion. This is usually administered by giving 1 vial per hour for 4 consecutive hours. Alternatively, 1 vial (50,000 MSD units) per hour may be given for 2 consecutive hours and repeated in 3 to 6 hours. The dosage range is 1 vial (50,000 MSD units) to 2 vials (100,000 MSD units) an hour by intravenous drip, for 1 to 6 hours, depending on the nature of the clot and the response

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of the patient. Most patients respond in one day; those who do not may require additional doses for three or four successive days.

*Patients not under active treatment with anticoagulants at the time of the thromboembolic episode:*

New clot formation is unlikely to occur during the administration of THROMBOLYSIN, so that anticoagulants may be unnecessary in this period. However, the fibrinolytic activity of THROMBOLYSIN persists only 3 to 4 hours after cessation of infusion; in patients subject to thrombosis, provision should be made to provide adequate therapeutic anticoagulant effect at this time.

*Patients under active treatment with anticoagulants:*

Within recommended dosages, THROMBOLYSIN produces only minor alterations in the clotting mechanism: the prothrombin time is generally increased by only a few seconds, the Lee-White clotting time by only 1 to 4 minutes, and the fibrinogen levels generally decrease by about 30 percent of control values. In themselves, these alterations are probably of no clinical significance. In patients on concurrent anticoagulant therapy in whom the clotting mechanism is depressed to midtherapeutic levels, the small additional depression due to THROMBOLYSIN should produce no added danger; however, the addition of THROMBOLYSIN may be hazardous when the therapeutic anticoagulant level already threatens to exceed safe limits.

#### *What Other Precautions are Necessary?*

THROMBOLYSIN is contraindicated in the presence of a hemorrhagic diathesis or hypofibrinogenemia. Fibrinolytic activity usually increases spontaneously for a short period after anesthesia or surgery. Therefore, THROMBOLYSIN should be used with caution because lysis of the clots at the operative site may occur.

Bleeding from open wounds or recent operative sites can occur during therapy. Usually this has been observed only in patients receiving both an anticoagulant and THROMBOLYSIN. In such cases, the bleeding was controlled by the use of plasma or whole blood transfusions. A specific antagonist to the anticoagulant may also be used.

#### *What Side Effects May Occur?*


Febrile reactions may occur, but these are rarely severe. When they do occur, the temperature usually rises rapidly to a peak, then returns to normal within 24 hours. In some patients, a rise in temperature above 1.5 to 2 degrees F. is accompanied by chills, nausea, vomiting, dizziness, headache, muscle pain, back pain, tachycardia, or hypotension.

*How is it Supplied?* 100-cc. vials containing 50,000 MSD units.

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Bibliography: 1. Lamphier, T. A., and Lyman, F. L.: J. Internat. Coll. Surgeons 31:420-423 (April) 1959. 2. Smigel, J. O.; Lowe, K. J.; Hosp, P. H., and Gibson, J. H.: M. Times 86:1521-1526 (Dec.) 1958.



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**References:** 1. Freed, S. C.: Psychic factors in the development and treatment of obesity, *J.A.M.A.* 133:369, Feb. 8, 1947. 2. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, Oct. 1958. 3. Plotz, M.: Modern management of obesity—the "social diet." *J.A.M.A.* 170:1513, July 25, 1959.

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# ANNALS OF INTERNAL MEDICINE

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## SODIUM AND WATER DIURESIS IN CIRRHOTIC PATIENTS WITH INTRACTABLE ASCITES FOLLOWING CHEMICAL INHIBITION OF ALDOSTERONE SYNTHESIS \*†

By DONALD A. HOLUB, M.D., and JOSEPH W. JAILER, M.D., Ph.D.,  
*New York, N. Y.*

CIRRHOSIS of the liver, in common with the nephrotic syndrome and congestive heart failure, is often complicated by the abnormal retention of sodium and water. The underlying pathophysiology is not completely understood, but factors such as hypoproteinemia, elevation in portal or systemic venous pressure, and changes in renal hemodynamics are now known to contribute to the sustained accumulation of sodium and water which is frequently seen in these diseases.

In addition, excessive amounts of a salt-retaining material are present in the urine of patients with hepatic cirrhosis and ascites.<sup>1</sup> This substance causes retention of sodium when injected into the adrenalectomized rat, and has been conclusively identified as aldosterone, the principal mineralocorticoid secreted by the human adrenal cortex.<sup>2,3,4</sup> Despite this association between clinical states of salt and water retention and the excessive excretion of aldosterone, the precise physiologic significance of "secondary" hyperaldosteronism is still far from clear. Variable and inconclusive results have been obtained following various measures designed either to reduce or

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Services of the Presbyterian Hospital and Francis Delafield Hospital, New York, N. Y.

† These studies were aided by Grant A 2208 from the National Institutes of Health, U. S. Public Health Service.

Requests for reprints should be addressed to Donald A. Holub, M.D., Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York 32, N. Y.

eliminate the secretion of aldosterone by the adrenal cortex (adrenalectomy, treatment with inhibitors of steroidal biosynthesis), or to antagonize the peripheral action of this hormone (aldosterone "antagonists" such as spironolactone).

The present study was undertaken in an attempt to delineate more precisely the role played by aldosterone in subjects with chronic liver disease and intractable ascites. Chemical inhibition of aldosterone biosynthesis was attempted in these patients by the administration of Su 4885 or 2-methyl-1,2-bis(3-pyridyl)-1-propanone. This compound is a recently synthesized analogue of amphenone B.<sup>6</sup> Unlike the latter substance, Su 4885 is relatively nontoxic, and is capable, when administered in the appropriate amounts, of selectively inhibiting the hydroxylation of position 11 on the steroid nucleus, presumably by direct action upon the 11 $\beta$ -hydroxylating enzyme within the adrenal cortex. Previous experience with this compound has demonstrated that it will inhibit the biosynthesis of 11-hydroxylated steroids such as hydrocortisone; as a result of such inhibition, the corresponding 11-desoxy steroids are synthesized and released into the circulation.<sup>6-8</sup> Since 11-desoxyhydrocortisone (compound S) is a relatively weak suppressor of pituitary ACTH secretion, ACTH release from the anterior pituitary gland is enhanced. The adrenal cortex is therefore stimulated to produce compound S in large quantity, two to four times greater than the amounts of hydrocortisone normally synthesized by the adrenal cortex. This is reflected by a rise in the excretion of urinary ketogenic steroids, since determination of the ketogenic steroids measures the metabolites of compound S in addition to those of hydrocortisone.

It was reasoned that the synthesis of aldosterone might also be inhibited by Su 4885 because aldosterone, like hydrocortisone, is hydroxylated at position 11. Inhibition of aldosterone production, if achieved by these means, might then be expected to reverse the accumulation of salt and water in patients with cirrhosis of the liver with ascites, if this accumulation is dependent upon aldosterone action.

#### MATERIALS AND METHODS

Eight patients with chronic liver disease were studied. Of these, four patients had Laennec's cirrhosis; two, cirrhosis of the postnecrotic variety; one, chronic passive congestion of the liver ("cardiac cirrhosis") associated with severe rheumatic heart disease, and one, the Budd-Chiari syndrome and hepatic cirrhosis. In five of the eight cases, specific histologic diagnoses were established by means of hepatic needle biopsy, laparotomy or post-mortem examination. All eight patients had significant ascites which was judged "intractable" on the basis of loss of responsiveness to dietary sodium restriction and also to mercurial and chlorothiazide diuretics. Detailed clinical information is summarized in table 1.

TABLE I  
Clinical Data on Patients Treated with Su 4885

Case	Diagnosis	Esophageal Varices	Bilirubin mg. %	Alkaline Phosphatase	BSP Retention % at 30 min.	Albumin gm. %	Globulin gm. %	Cephalin Flocculation	Thymol Turbidity	Cholesterol Total/Esters mg. %	BUN mg. %
1 22 ♀	Chiari's syndrome; cirrhosis*	No	1.6	15.6 (K.A.)	30	3.8	1.3	0	0	229/172	15
2 60 ♂	Laennec's cirrhosis	Yes	0.9	12.0 (K.A.)	55	2.6	3.9	3+	3+	162/122	14
3 60 ♀	Laennec's cirrhosis*	Yes	Trace	26.0 (K.A.)	25	1.9	3.3	0	0	184/118	12
4 53 ♂	Postnecrotic cirrhosis*	No	Trace	Normal	5	Slight decrease†	Slight increase†	±	0	—	31 (NPN)
5 49 ♀	Postnecrotic cirrhosis*	Yes	0.4	7.5 (B.U.)	20	Slight decrease†	Increase†	3+	9 u.	223/145	17 (NPN)
6 61 ♀	Laennec's cirrhosis*	Yes	1.1	Normal	37	Normal†	Increase†	±	0	223/131	36 (NPN)
7 59 ♀	Cardiac cirrhosis	No	1.1	7 (K.A.)	30	2.5	5.3	0	0	147/—	55
8 55 ♂	Laennec's cirrhosis	Yes	3.8	—	40	1.9	4.3	2+	2+	157/107	16

\* Diagnosis proved histologically.

† Visual comparison with normal serum pool following electrophoretic separation and staining with bromphenol blue.

Balance studies were performed on the Metabolic Wards at the Presbyterian and Delafield Hospitals. Completeness of urine collections was checked by determining the creatinine content of each specimen. Urinary sodium and potassium concentrations were determined by means of flame photometry. Urinary 17-hydroxycorticosteroids were measured by a modification of the ketogenic method of Norymberski.<sup>9</sup> Urinary aldosterone excretion was determined by the method of Sobel et al.; normal values using this method range between 2 and 15  $\mu$ g. per day.<sup>10</sup>

Su 4885 was administered orally in doses of 750 mg. every four hours. Although the ingestion of this compound was occasionally followed by transient dizziness and/or dyspepsia, in no case was cessation of Su 4885 treatment necessary because of these side-effects. Prednisone was administered orally in doses of 10 mg. three times a day. SC9420 or spironolactone (3-(3-oxo-7 $\alpha$ -acetylthio-17 $\beta$ -hydroxy-4-androsten-17 $\alpha$ -yl) propionic acid  $\gamma$ -lactone) was administered to case 4 orally in the dosage of 100 mg. four times a day.

Tetrahydrocortisone (THE), tetrahydro-hydrocortisone (THF), tetrahydrodesoxycorticosterone (THDOC), and tetrahydro-11-desoxyhydrocortisone (THS) were identified on the basis of running rates identical to those of authentic standards in two paper chromatographic systems, and the expected reactions with blue tetrazolium and Porter-Silber reagents.

## RESULTS

1. *Patients Treated with Su 4885 Alone:* The effect of Su 4885 given without any other medication was assessed in three patients with intractable ascites (table 2). The first patient, a 19 year old female with the Budd-Chiari syndrome and cirrhosis of the liver (case 1), had a urinary aldosterone excretion of 29 micrograms per day and a urinary sodium excretion of less than 4 mEq. per day prior to Su 4885 treatment. The drug was then administered over a 48-hour period, and a gradual increase in the amount of urinary sodium was observed beginning 48 hours after the last dose, rising gradually to a peak of almost 100 mEq. of sodium per day (figure 1). A water diuresis also occurred, as indicated by a weight loss of approximately six pounds. Aldosterone excretion during the period of maximal sodium diuresis fell to 3  $\mu$ g. per day. During the period of Su 4885 administration, the expected rise in urinary ketogenic steroids was observed; these steroids fell to rather low levels during the period of salt and water diuresis. Approximately one month following the completion of this study, the same patient was given another two-day course of Su 4885, and once again demonstrated a diuresis of sodium and of water entirely comparable to that shown in figure 1.

Because of the impressive results obtained on two different occasions in this first patient, two additional patients were given Su 4885, and mani-

TABLE 2  
Effect of Su 4885 on Urinary Electrolyte and Steroid Excretion in Patients  
with Intractable Ascites

Day	Regimen	Volume ml./day	Na + mEq./day	K + mEq./day	Na/K Ratio	17KGS mg./day	Aldosterone μg./day
Case 1, 19, female, Budd-Chiari syndrome, ascites; sodium intake, 12 mEq.							
1	0	475	1.3	53.1	.02	4.7	29
2	0	485	3.5	44.6	.08	4.5	
3	Su 4885, 500 mg. every 4 hrs. p.o.	530	1.9	30.7	.06	13.1	
4		510	5.8	44.1	.13	15.1	
5		430	2.1	32.5	.06	7.2	
6	0	470	2.6	37.6	.07		
7	0	500	18.0	37.8	.48		
8	0	500	16.0	47.8	.33	2.6	
9	0	500	16.0	58.9	.27		
10	0	625	41.8	64.3	.65		
11	0	675					
12	0	800	94.4	50.0	1.89	3.3	3
13	0	615	38.7	36.7	1.05		
14	0	875	69.1	72.7	.95		
15	0	840	90.7	53.8	1.69		
16	0	740	27.1	75.8	.36		
17	0	750	32.6	67.5	.48	4.6	
18	0	800	24.0	78.4	.31		
Case 2, 66, male, Laennec's cirrhosis, ascites; sodium intake, 12 mEq.							
1	0	1,380	1.2	89.6	.01	7.2	19
2	0	1,500	2.2	111.0	.02	19.0	
3	0	860	1.9	110.0	.02	8.8	
4	Su 4885, 500 mg. every 4 hrs. p.o.	1,300	1.0	104.1	.01	14.5	
5		1,720	2.0	119.8	.02	22.8	
6		1,720	1.3	148.9	.01	48.3	3
7		820	1.1	79.0	.01	28.0	
8	0	840	1.4	83.8	.01	29.1	
9	0	1,300	1.7	119.8	.01	19.9	
10	0	1,640	2.2	135.2	.02	16.5	
11	0	1,640	2.6	138.0	.02	14.5	
12	0	1,400	1.7	119.2	.01	14.1	
13	0	1,400	1.8	116.6	.02		
14	0	1,340	2.1	102.8	.02	17.4	90
Case 3, 48, female, Laennec's cirrhosis, ascites; sodium intake, 12 mEq.							
1	0	1,120	0.8	17.5	.05	5.7	
2	0	960	0.8	17.3	.05	8.6	
3	0	540	0.4	13.1	.03	4.2	
4	0	1,000	0.9	20.5	.04	8.1	
5	0	950	1.0	22.0	.05	3.6	
6	Su 4885, 500 mg. every 4 hrs. p.o.	1,500	1.0	30.8	.03	11.1	
7		960	0.3	34.6	.01	23.2	
8	0	1,180	0.4	41.1	.01	9.9	
9	0	1,220	0.8	30.2	.03	7.8	
10	0	1,680	1.4	52.1	.03	10.1	
11	0	1,760	1.5	49.2	.03	6.0	
12	0	1,460	2.0	56.4	.04	7.5	
13	0	1,680	1.1	68.8	.02	7.4	

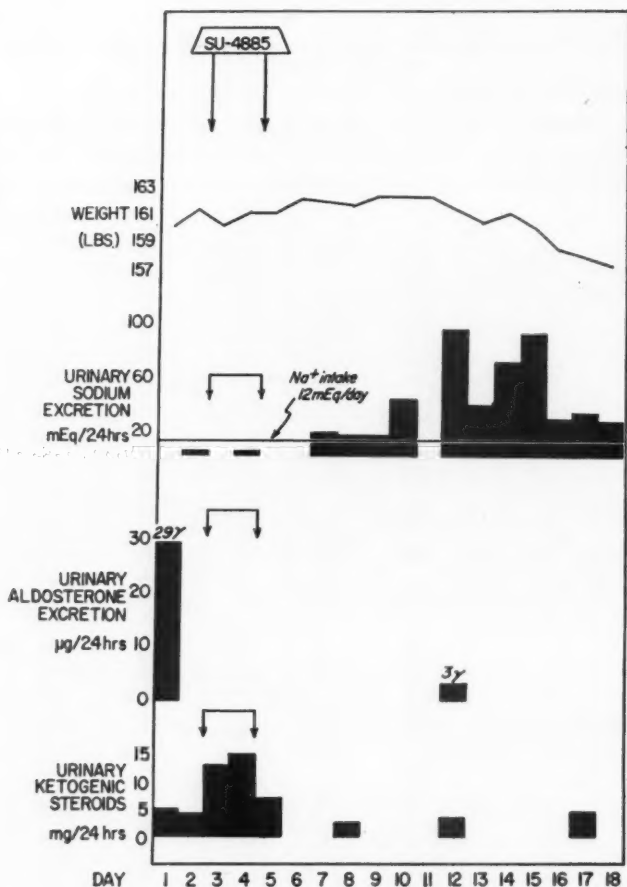


FIG. 1. Case 1, 19 year old white female with Chiari's syndrome. Two-day course of Su 4885 produced a gradual rise in urinary sodium excretion, significant weight loss, fall in aldosterone excretion and transient elevation of urinary ketogenic steroids.

tested completely different responses (table 2). Figure 2 demonstrates the data on one of these patients (case 2). Administration of Su 4885 over a four-day period produced a brisk rise in the urinary ketogenic steroids, as expected, and a fall in aldosterone from 19 to 3 µg. per day. However, this patient continued to retain sodium avidly, and his weight was unchanged. The failure of Su 4885 to achieve a salt and water diuresis in this patient, despite apparent success in inhibition of aldosterone synthesis, raised the possibility that a salt-retaining hormone other than aldosterone was being synthesized and excreted by him. Chromatographic analysis of this patient's



urine revealed the presence, during the period of Su 4885 administration, of large quantities of a steroid identified as tetrahydrodesoxycorticosterone (THDOC), the metabolic product of 11-desoxycorticosterone (DOC). THDOC was present in the urine only during the period of Su 4885 ingestion, and was absent one week later, at which time the aldosterone excretion had risen to 90  $\mu$ g. per day.

The third patient (case 3) also failed to respond to Su 4885 with either sodium or water diuresis, although a rise in urinary ketogenic steroids was observed, indicating that Su 4885 was acting upon the adrenal cortex. Large quantities of THDOC were found in the urine of this patient during the period of Su 4885 administration.

2. *Patients Treated with Su 4885 and Prednisone:* The effect of Su 4885 when administered concurrently with prednisone was observed in five patients with intractable ascites. The relevant data for three of these pa-

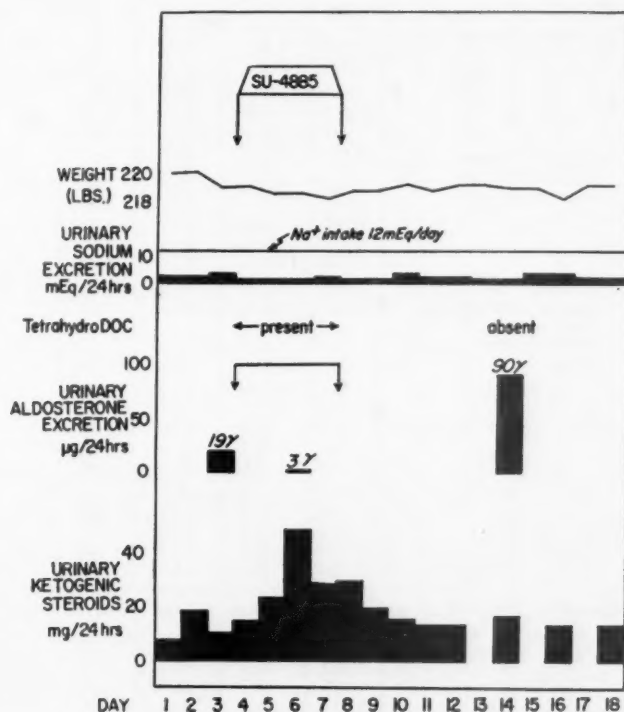


FIG. 2. Case 2, 66 year old white male with Laennec's cirrhosis. No increase in sodium excretion or fall in weight followed Su 4885 administration, despite inhibition of aldosterone synthesis. Note presence of THDOC during Su 4885 treatment, and absence from urine seven days later.

TABLE 3  
Effect of Su 4885, with and without Prednisone, on Urinary Electrolyte and Steroid Excretion in Three Patients with Intractable Ascites

Day	Regimen	Volume ml./day	Na + mEq./day	K + mEq./day	Na/K Ratio	17 KGS mg./day	Aldo- sterone μg./day
Case 4, 54, male, postnecrotic cirrhosis, ascites; sodium intake, 12 mEq.							
1	0	820	0.6	23.5	.02		
2	0	1,327	1.6	18.2	.09		
3	0	971	0.5	13.8	.04	2.4	
4	Su 4885, 500 mg. every 4 hrs. p.o.	1,692	1.7	14.4	.13		
5		1,661	1.2	24.1	.05	62.0	
6		1,700	1.9	23.1	.08		
7		814	1.1	11.9	.09		
8	0	1,680	1.8	33.8	.05		
9	0	1,104	1.5	12.7	.12		
1	0	2,255	2.5	60.0	.04	9.4	
2	0	2,012	2.4	50.7	.05	8.1	
3	0	2,465	2.2	40.2	.06		23
4	Prednisone, 10 mg. t.i.d.	3,278	3.3	60.0	.05		
5		3,000	4.8	50.1	.10		
6		3,180	6.7	55.0	.12	14.5	
7		3,000	4.5	57.6	.08		26
8	Prednisone, 10 mg. t.i.d., and Su 4885, 500 mg. every 4 hrs. p.o.	3,540	49.2	59.5	.83		
9		4,057	114.0	64.1	1.78	19.6	
10		4,184	111.3	67.4	1.65		9.6
11		4,480	125.0	73.0	1.71		
12		5,335	137.6	89.6	1.54		
13		4,960	153.3	79.9	1.92	16.8	
14		4,737	134.5	77.2	1.74		
15		4,780	124.3	65.0	1.91		
16	Prednisone, 10 mg. t.i.d., and Su 4885, 500 mg. every 4 hrs. p.o., plus SC9420, 100 mg. every 6 hrs.	4,375	136.1	80.9	1.68		
17		4,366	142.3	93.9	1.52		
18		5,060	162.9	64.8	2.52		
19		5,661	228.1	76.4	2.99		
20	Prednisone, 10 mg. t.i.d.	4,833	151.8	88.9	1.71		
21		3,760	21.4	75.9	.28		
22		3,640	7.6	71.0	.11		
23		3,660	6.2	71.4	.09		
24		3,470	5.6	63.5	.09		
25	0	3,250	3.3	35.4	.09		
26	0	3,200	2.6	52.8	.05		
27	0	2,900	2.3	72.5	.03		
28	0	2,500	1.8	37.3	.05		
29	0	3,200	2.2	63.0	.04		
Case 5, 49, female, Laennec's cirrhosis, ascites; sodium intake, 12 mEq.							
1	0	1,388	8.2	32.2	.25		
2	0	1,867	15.5	30.3	.51		
3	0	1,475	11.7	28.0	.42	7.9	
4	0	1,812	20.8	31.7	.66	12.1	
5	Su 4885, 500 mg. every 4 hrs. p.o.	1,070	3.0	22.1	.14	10.5	
6		1,857	3.2	29.0	.11	43.4	
7		1,908	3.1	27.9	.11		
8		840	4.5	26.6	.17	31.4	

TABLE 3—Continued

Day	Regimen	Volume ml./day	Na+ mEq./day	K+ mEq./day	Na/K Ratio	17 KGS mg./day	Aldo- sterone µg./day
9	0	1,500	2.9	26.9	.11		
10	0	1,330	5.5	15.3	.36		
11	0	1,832	12.3	13.0	.94	9.8	
12	0	2,065	10.7	10.9	.98		
1	0	1,174	9.5	28.2	.34	6.8	
2	0	1,183	3.2	21.1	.15		
3	0	566	4.5	26.5	.17		12
4	0	833	5.9	23.1	.26	2.4	
5	0	936	3.7	19.9	.19	9.7	
6	Prednisone, 10 mg. t.i.d.	1,828	28.0	23.6	1.19		
7		1,017	30.9	24.7	1.25	9.8	
8		1,895	43.6	24.6	1.77		
9		980	33.7	17.5	1.92	9.3	
10	Prednisone, 10 mg. t.i.d., and Su 4885, 500 mg. every 4 hrs.	1,480	37.3	14.2	2.52		5
11		1,835	37.8	12.9	2.94	7.9	
12		1,596	61.9	14.7	4.20	13.9	
13		1,916	75.5	15.9	4.75	11.6	
14	Prednisone, 10 mg. t.i.d.	1,784	86.5	20.5	4.21	11.7	3
15		2,338	112.4	30.1	4.05		
16		1,260	54.5	30.1	1.81		
17		1,869	58.3	41.9	1.38	9.7	
18	0	1,892	41.4	29.2	1.42		
19		1,540	19.3	25.0	.77		
20		1,100	5.3	15.0	.35		
21		1,220	8.1	24.0	.33		
22	0	1,126	1.9	18.1	.11		

Case 6, 42, female, Laennec's cirrhosis, ascites; sodium intake, 12 mEq.

1	0	1,085	2.0	26.9	.07		
2	0	930	2.2	23.7	.09		
3	0	980	1.6	31.4	.05	7.4	
4	0	1,000	2.8	32.2	.08		
5	0	980	2.1	34.8	.06	6.6	
6	Prednisone, 10 mg. t.i.d.	1,665	12.8	49.1	.26		
7		2,180	25.3	49.5	.51		
8		2,170	44.7	32.6	1.37	9.2	
9		1,962	25.7	44.3	.58		
10	Prednisone, 10 mg. t.i.d., and Su 4885, 500 mg. every 4 hrs.	2,067	41.5	40.7	1.02	5.8	
11		2,250	79.7	35.1	2.27		
12		2,999	111.0	43.2	2.57	10.4	
13		2,809	94.4	42.1	2.24		
14	Prednisone, 10 mg. t.i.d.	2,616	82.1	37.1	2.21	8.4	
15		1,916	49.0	46.6	1.05		
16		1,719	62.6	48.0	1.30		
17		2,086	39.2	51.3	.76	9.7	
18	0	1,673	21.4	48.5	.44		
19		1,976	27.4	46.2	.59		
20		1,450	7.2	26.6	.27		
21		764	5.0	35.1	.14		
22	0	1,129	7.5	47.4	.16		
23	0	1,161	4.2	40.1	.10		
24	0	1,022	5.2	36.0	.14		
25	0	1,149	3.7	36.7	.10		

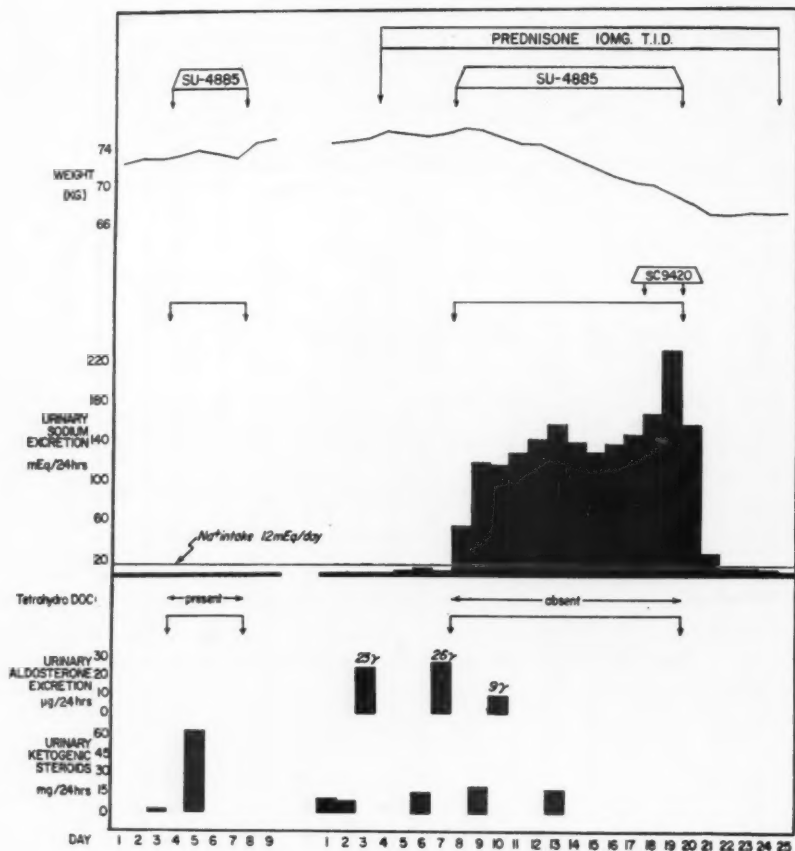


FIG. 3. Case 4, 54 year old white male with postnecrotic cirrhosis. Induction of successful diuresis of sodium and water following combined treatment with Su 4885 and prednisone. Absent THDOC and lack of rise in ketogenic steroids during combined treatment period demonstrate pituitary suppression by prednisone. Note failure of treatment with Su 4885 alone to produce sodium diuresis or weight loss.

tients are presented in table 3. Case 4, a 54 year old male with documented postnecrotic cirrhosis and ascites, was given two courses of Su 4885 (figure 3). During the first part of the study, on Su 4885 treatment alone, urinary sodium content did not rise above the base line levels of 1 to 2 mEq. per day. The urinary ketogenic steroids rose sharply; as with cases 2 and 3 (vide supra), THDOC was demonstrated in the urine of case 4 in large quantity during this period. During the next phase of the study, prednisone was administered and produced relatively no change in urinary sodium excretion or in body weight. With the addition of Su 4885 to the regimen for a

period of 12 days, the urinary sodium excretion rose to the 120- to 155-mEq. range; this was associated with the diuresis of water and loss of approximately 12 pounds in weight. Aldosterone excretion was effectively inhibited by Su 4885, falling from 26 to 9  $\mu$ g. per day. Moreover, THDOC was not present in the urine during this period of combined treatment, presumably because prednisone effectively suppressed the release of ACTH by the anterior pituitary gland.

During the last two days of the combined therapy, the patient was given SC9420 or spironolactone, a compound which acts as a peripheral antagonist

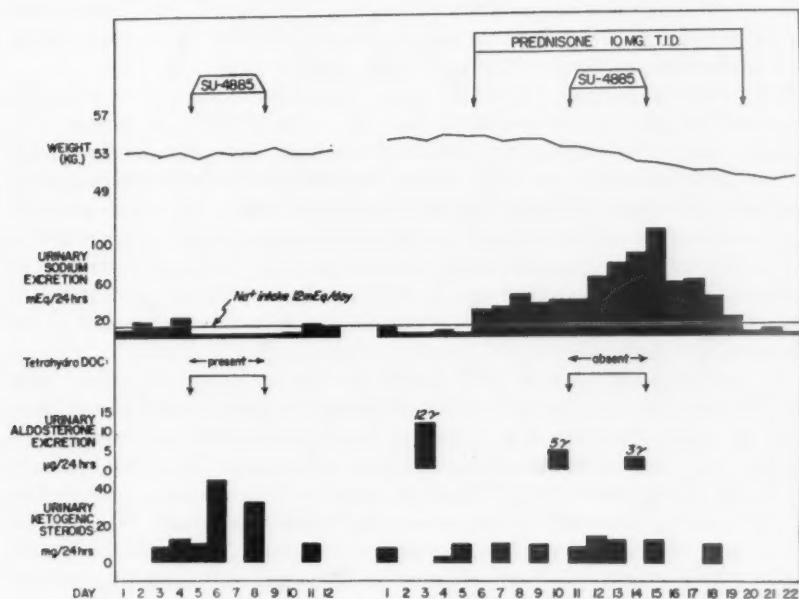


FIG. 4. Case 5, 49 year old Negro female with Laennec's cirrhosis. Combined Su 4885-prednisone regimen produced diuresis of sodium and water after failure of Su 4885 treatment alone. Note effect of prednisone on urinary THDOC and ketogenic steroids during Su 4885 administration.

of aldosterone by competitive inhibition, probably at the level of the renal tubule. During this period the urinary sodium excretion rose to 226 mEq. per day. Following termination of Su 4885 and SC9420 administration, the patient again entered a phase of sodium retention, although prednisone treatment was continued.

Combined Su 4885 and prednisone treatment also proved effective in case 5, a 49 year old woman with Laennec's cirrhosis (figure 4). Treatment with Su 4885 alone failed to increase urinary sodium excretion or to

promote water diuresis. On the contrary, sodium retention seemed more pronounced during the period of Su 4885 administration; large quantities of THDOC were measured in the urine during this phase of the study. Prednisone was then given for a 14-day period, during the middle of which the patient also received Su 4885 for four days. With prednisone alone, the urinary sodium excretion increased to 25 to 40 mEq. per day. However, when Su 4885 and prednisone were given concurrently, the urinary sodium excretion increased to a peak of 110 mEq. per day; this was associated with an increase in urinary volume and significant loss in weight. No rise in urinary ketogenic steroids was observed, illustrating the effectiveness of prednisone as an inhibitor of pituitary ACTH release. This action of prednisone was confirmed by the absence of THDOC from the urine of this patient during the period of combined therapy.

The third patient in this group (case 6) was a 42 year old woman with Laennec's cirrhosis and ascites (table 3). On prednisone therapy the urinary sodium excretion was increased from the 1-3-mEq.-per-day range to levels of 13-45 mEq. per day. When Su 4885 was added to this regimen, the urinary sodium excretion rose to a peak of 111 mEq. of sodium per day, and this was associated with a significant diuresis of water. During this period the urinary ketogenic steroids failed to rise, demonstrating the inhibitory effect of prednisone upon ACTH release. Upon termination of Su 4885 administration, the urinary sodium excretion fell into the 20- to 40-mEq.-per-day range.

Two additional patients with intractable ascites (cases 7 and 8) were studied with the combined Su 4885-prednisone regimen. Neither of these patients demonstrated a rise in urinary sodium excretion or manifested a weight loss, despite evidence that therapeutic levels of Su 4885 had been achieved (appearance of THS and decrease in hydrocortisone metabolites in the urine), and that ACTH release had been successfully prevented by prednisone (failure of the urinary ketogenic steroids to rise following Su 4885 administration). Both of these patients had profound hypoproteinemia, in contrast to the patients who were successfully diuresed with the combined regimen; case 7 was azotemic as well (table 1).

#### DISCUSSION

Chart and Shipley demonstrated in 1953 that patients with cirrhosis of the liver and ascites excreted in their urine large quantities of a sodium-retaining substance.<sup>1</sup> This observation has been repeatedly confirmed since, and the sodium-retaining material has been identified as aldosterone in several laboratories.<sup>2-4</sup> Patients with cirrhosis but without fluid retention usually do not demonstrate this increase in urinary aldosterone. It has been demonstrated recently that the rate of aldosterone secretion by the adrenal cortex over a 24-hour period is distinctly elevated above normal in patients



with cirrhosis and ascites.<sup>11,12</sup> Aldosterone levels in plasma are similarly increased above normal in these patients.<sup>12</sup> The latter abnormality, a direct consequence of the increased aldosterone secretion rate, may also reflect a decrease in the rate of inactivation of aldosterone by the pathologic liver.<sup>13</sup>

Since the physiologic mechanisms which control aldosterone synthesis and secretion are still speculative, the cause of the increased aldosterone levels in patients with cirrhosis and ascites is not known. It has been postulated that a contributory factor in such patients is diminished effective intravascular volume.<sup>14-15</sup> There is no convincing direct evidence in support of this hypothesis, however; somewhat paradoxically, perhaps, total body water and plasma volume are elevated in patients with hepatic cirrhosis.<sup>16-17</sup>

In the present series of patients, aldosterone excretion was increased above normal limits in three of the four patients in whose urine the hormone was measured. As Peterson has indicated recently, urinary aldosterone values may not always accurately reflect the secretory activity of the adrenal cortex, since the usual technics for urinary aldosterone determination measure less than 5% of the steroid actually secreted by the adrenal glands.<sup>12</sup> Although the majority of cirrhotic patients with ascites and/or restricted sodium intake will manifest both increased urinary aldosterone excretion and increased aldosterone secretory rates, the former parameter is proportionately much less elevated than the latter. This imperfect correlation between aldosterone secretion and excretion has also been observed in patients with primary hyperaldosteronism.<sup>11</sup> It is probable, therefore, that all of the patients in the present study were secreting excessive amounts of aldosterone.

The precise role which secondary hyperaldosteronism plays in states of sodium and water retention is not known. Improvement in such states following bilateral adrenalectomy has been adduced as evidence that hyperaldosteronism exerts an important influence in the pathogenesis of sodium retention. Adrenalectomy has been shown to produce sodium diuresis and control of fluid retention in dogs with experimentally induced ascites,<sup>18</sup> and in patients with congestive heart failure<sup>19</sup> and hepatic cirrhosis with ascites.<sup>20-22</sup> Baronofsky and his colleagues found that adrenalectomized cirrhotic patients continue to retain sodium and water following excessive sodium dietary intake, but that such retention is reversed easily following dietary sodium restriction.<sup>22</sup> These patients do not develop ascites on ordinary sodium intake. However, that these patients were able to retain sodium at all in the absence of urinary aldosterone led the authors to conclude that mechanisms for sodium retention other than those involving aldosterone exist in man.

The successful diuresis of ascites which has been achieved through the use of the spiro lactone compounds, such as SC9420, also attests to the importance of increased production of aldosterone in states of sodium and

water retention. Unlike Su 4885, the spiroactones do not diminish aldosterone synthesis, but have been shown to act as peripheral antagonists of aldosterone, supposedly competitively inhibiting aldosterone at its site of action in the renal tubule. Absence of kaliuresis has been characteristic of the natriuresis produced by the spiroactones.<sup>23-26</sup>

The development of Su 4885 has provided a convenient and relatively nontoxic means for the temporary interruption of steroidal biosynthesis by the adrenal cortex. Unlike its precursor and analogue, amphenone B, Su 4885 inhibits the adrenal 11 $\beta$ -hydroxylating enzyme with relative specificity in the doses which have been employed clinically. The most obvious and striking effect of Su 4885 is the decrease in excretion of hydrocortisone metabolites (THE, THF) in the urine, coincident with the appearance of large quantities of THS, the major metabolite of 11-desoxyhydrocortisone. Inhibition of hydrocortisone synthesis results in augmented secretion of ACTH from the anterior pituitary gland.<sup>6</sup> In normal individuals, therefore, the adrenal cortex is stimulated to produce even greater quantities of steroids. With the persisting Su 4885-induced block of 11 $\beta$ -hydroxylation, the adrenals release primarily 11-desoxy steroids into the circulation. Aldosterone, which, like hydrocortisone, bears a hydroxyl atom at position 11, would logically appear to be susceptible to the inhibiting influence of Su 4885.

In the present study, all of the four patients in whom aldosterone levels were determined in the urine demonstrated decreases in these levels following Su 4885 administration. Similar results have been obtained by Salassa and Mattox<sup>27</sup> and Coppage et al.<sup>28</sup> in patients with primary hyperaldosteronism and secondary hyperaldosteronism, and in normal subjects with high aldosterone levels secondary to restricted dietary sodium. Conversely, Jenkins et al.<sup>29</sup> were unable to reduce aldosterone excretion in two patients employing Su 4885, and Gold et al.<sup>30</sup> reported that a patient with an aldosterone-secreting adrenocortical adenoma actually increased the excretion of aldosterone following the injection of Su 4885.

Of the first three patients treated with Su 4885 in the present study, only one responded with a significant diuresis of sodium and water. The failure of two of these subjects to exhibit the expected sodium diuresis following inhibition of aldosterone excretion was puzzling until a more detailed study of the steroidal metabolites in the urine was undertaken. Large quantities of THDOC were found to be present in the urine of these two patients (and subsequent patients) during the period of Su 4885 administration. Under the influence of Su 4885, the adrenal cortex produced impressive quantities of DOC, the 11-desoxy analogue of corticosterone. Corticosterone, which, unlike DOC, possesses relatively minor mineralocorticoid properties, is a naturally occurring product of the adrenal cortex. DOC, on the other hand, is probably not secreted by the adrenal gland, although it has been

used for many years in the treatment of adrenal insufficiency because of its potent sodium-retaining properties.

Patients treated with Su 4885 therefore respond with at least three major changes in steroidal secretion (figure 5). 11-desoxy-hydrocortisone is produced in place of hydrocortisone, with the resultant increase in circulating ACTH and increased stimulation of the adrenal cortex. Corticosterone secretion is inhibited by Su 4885 and is replaced by DOC, which is produced in large quantities under these conditions of excessive ACTH stimulation. Finally, aldosterone synthesis is inhibited by Su 4885; the 11-desoxy analogue of aldosterone has not been identified as yet.

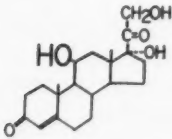
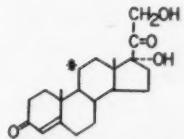
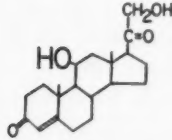
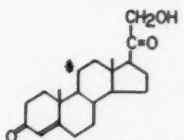
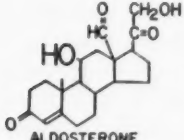
MAJOR ADRENAL STEROIDS	EFFECT OF SU-4885 ON STEROID STRUCTURE	RELATED PHYSIOLOGICAL EFFECTS OF SU-4885
 HYDROCORTISONE Compound F	 11-DESOXYHYDROCORTISONE Compound S	Diminished inhibition of ACTH release → increased circulating levels of ACTH → stimulation of the adrenal cortex.
 CORTICOSTERONE Compound B	 11-DESOXYCORTICOSTERONE DOC	Sodium retention
 ALDOSTERONE	?	Sodium excretion

FIG. 5. Summary of chemical and physiologic effects of Su 4885. The 11-desoxy analogue of aldosterone has not yet been identified.

Electrolyte balance in a patient receiving Su 4885 therefore reflects the balance of these various alterations in steroidal production. Inhibition of aldosterone synthesis results in sodium excretion and, when this is the predominant effect (as in case 1), leads to negative sodium balance and significant diuresis. However, in other—and perhaps the majority of—patients treated with Su 4885, the production of DOC and the resultant

tendency toward sodium conservation are enough to negate the sodium-losing effect of aldosterone inhibition. This would explain the failure of cases 2 and 3 to demonstrate sodium diuresis on Su 4885.

Since the production of DOC appears to be under the control of ACTH, inhibition of ACTH secretion by the anterior pituitary gland might reasonably be expected to reduce DOC secretion, and thus to allow the aldosterone-inhibiting effect of Su 4885 to predominate. Such inhibition of ACTH production was achieved in cases 4, 5 and 6 by the administration of prednisone. Subsequent administration of Su 4885 in these patients produced inhibition of aldosterone excretion but little or no secretion of DOC. Under these conditions, natriuresis occurred together with an associated water diuresis. Coppage et al., in a recent study employing similar conditions, were also able to achieve increases in sodium excretion in cirrhotic patients, but these were very small in magnitude and were not associated with clinically significant diuresis of water.<sup>28</sup>

In contrast to diureses achieved with mercurial diuretics or agents such as chlorothiazide, diuresis of sodium which resulted from the combined Su 4885-prednisone regimen was not associated with either significant urinary loss of potassium or fall in serum potassium levels. This observation is consistent with the postulated mechanism of action of aldosterone, i.e., the facilitation of sodium reabsorption by the renal tubule, with secretion of potassium into the tubular urine. Sodium diuresis resulting from aldosterone inhibition would therefore be expected to result in potassium retention rather than in potassium diuresis, similar to that exhibited by a patient reported recently with isolated hypoaldosteronism.<sup>31</sup> Perhaps because of the relatively brief periods of induced hypoaldosteronism in this series, hyperkalemia was not observed.

The inhibition of aldosterone achieved by Su 4885 was not complete in any patient. Although aldosterone fell to low levels, in no instance did this hormone disappear completely from the urine. Further evidence bearing on this point was obtained in case 4, in whom the administration of the spironolactone, SC9420, superimposed upon Su 4885 and prednisone treatment, resulted in a further increase in urinary sodium excretion and a more rapid fall in body weight. SC9420 has been demonstrated to be ineffective as a sodium diuretic in the absence of aldosterone or other mineralocorticoid.<sup>32</sup> SC9420 presumably would have had no clinical effect in this patient if aldosterone synthesis had been completely inhibited by Su 4885. It is possible that more nearly complete inhibition of aldosterone production may be achieved with the use of larger doses of Su 4885 than have been employed in this study.

Cases 7 and 8 did not demonstrate any sodium diuresis on the combined Su 4885-prednisone regimen. A possible explanation is that sufficient aldosterone was produced by these patients, despite the administration of Su 4885, to maintain them in states of sodium retention. However, these

patients had markedly decreased serum albumins (2.5 and 1.9 gm.%, respectively), and it is quite possible that the oncotic pressures within their intravascular compartments were too low to sustain a diuresis, even if complete inhibition of aldosterone synthesis had been achieved. It seems quite unlikely that aldosterone is the sole regulator of sodium balance in man.

Prednisone, given alone, produced small increments in urinary sodium in only two of the five patients so studied. Neither of these two patients (cases 5 and 6) displayed an associated diuresis of water. Some workers have reported previously that prednisone was capable of causing the diuresis of both sodium and water in patients with cirrhosis and ascites.<sup>33-35</sup>

In view of the relative complexity of combined Su 4885-prednisone administration, and of the present unavailability of adequate supplies of Su 4885, it is not anticipated that the chemical inhibition of aldosterone production as achieved in the present study will be of immediate practical importance in the management of states of sodium and water retention. However, occasional patients with such conditions who become refractory to usual diuretic measures may respond to this regimen. A more fundamental aspect of this investigation is the demonstration that control of aldosterone synthesis is associated with changes in sodium and water balance in some patients with secondary hyperaldosteronism. Of the many factors known to contribute to the abnormal retention of sodium and water in patients with cirrhosis, the nephrotic syndrome and congestive heart failure, it would appear that the production of excessive amounts of aldosterone is of considerable importance.

#### SUMMARY

1. Su 4885, an inhibitor of the enzyme responsible for  $11\beta$ -hydroxylation within the adrenal cortex, was administered to eight patients with hepatic cirrhosis, intractable ascites and "secondary" hyperaldosteronism. Aldosterone synthesis was effectively diminished by this compound; however, the adrenal cortex produced large quantities of 11-desoxycorticosterone (DOC) under the influence of Su 4885.

2. The net effect of aldosterone inhibition and DOC production was continued retention of sodium and water in seven of eight patients. However, when suppression of ACTH release was achieved by the administration of prednisone, Su 4885 treatment resulted in inhibition of aldosterone synthesis without concurrent stimulation of DOC synthesis. Significant diuresis of sodium and water was produced by combined treatment with Su 4885 and prednisone in three of five patients. Urinary sodium excretion rose from less than 5 mEq. per day to values of over 100 mEq. per day in the patients who responded to this regimen.

3. It is concluded that the hypersecretion of aldosterone plays a significant role in the pathogenesis of sodium and water retention in many patients with hepatic cirrhosis and ascites.

## ACKNOWLEDGMENTS

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The advice of Dr. Andrew G. Frantz concerning chromatographic technics is gratefully acknowledged.

## SUMMARIO IN INTERLINGUA

Ben que hypersecretion de aldosterona occorre in patientes con cirrhosis e ascites, le signification physiologic de iste hyperaldosteronismo "secundari" non es cognoscite. In le presente studio, alterationes del synthese de aldosterona in subjectos cirrhotic esseva producite per le administration de un composito (Su 4885) que inhibi le 11(beta)-hydroxylation in le cortice adrenal human. Le effectos exercite per iste inhibition chimic de aldosterona super le metabolismo de electrolytos e de aqua esseva observate in patientes con cirrhosis de Laennec o cirrhosis post-necrotic e ascites de character intractabile.

Quando administrate sol, Su 4885 produceva un frappante reduction del excretion de aldosterona. Tamen, inter le octo patientes studiate, septe non reageva per diuresis de natrium o de aqua. Le analyse chromatographic del steroides urinari excernite durante le administration de Su 4885 revelava le presentia de grande quantitates de tetrahydrodisoxycorticosterona, le producto metabolic de disoxycorticosterona (DOC). Su 4885, ben que illo inhibi le formation de aldosterona, promove le production de DOC que es etiam un potente retentor de sal. Le resultado de iste processos es in le majoritate del patientes un continueate retention de natrium e de aqua.

Tamen, si le secretion de ACTH es prevenite per le administration de prednisona, le activitate adreno-cortical es supprime, e DOC non es formate in responsa a Su 4885. Tres patientes, refractori a Su 4885 sol, respondeva con frappante grado de diuresis de natrium e aqua al combinate administration de Su 4885 e prednisona. Un patiente, mantenite con iste programma durante 10 dies, augmentava su excretion urinari de natrium ab inter 0 e 2 ad inter 115 e 155 mEq per die e perdeva 19 libras de peso durante iste intervallo. In omne le patientes le cessation del therapia a Su 4885 resultava in le immediate reversion al nivellos pre-tractamental del excretion de natrium, in despecto del continueate administration de prednisona.

Iste studio demonstra que le regulation del synthese de aldosterona es associate con alterationes in le balancia de natrium e aqua in certe patientes con hyperaldosteronismo. Es concludite que le hypersecretion de aldosterona ha un rolo significative in le pathogenese del retention de natrium e de aqua in multe patientes con cirrhosis hepatic e ascites.

## BIBLIOGRAPHY

1. Chart, J. J., and Shipley, E. S.: Mechanism of sodium retention in cirrhosis of liver, *J. Clin. Investigation* 32: 560, 1953.
2. Axelrad, B. J., Cates, J. E., Johnson, B. B., and Luetscher, J. A., Jr.: Aldosterone in urine of normal man and of patients with oedema: its increased recovery after hydrolysis with acid and  $\beta$ -glucuronidase, *Brit. M. J.* 1: 196, 1955.
3. Wolff, H. P., Koczorek, Kh. R., Jesch, W., and Buchborn, E.: Untersuchungen über die Aldosteronausscheidung bei Leberkranken, *Klin. Wchnschr.* 34: 366, 1956.
4. Dyrenfurth, I., Stacey, C. H., Beck, J. C., and Venning, E. H.: Aldosterone excretion in patients with cirrhosis of the liver, *Metabolism* 6: 544, 1957.
5. Chart, J. J., Sheppard, H., Allen, M. J., Bencze, W. L., and Gaunt, R.: New amphenone analogs as adrenocortical inhibitors, *Experientia* 14: 151, 1958.



6. Liddle, G. W., Island, D., Lance, E. M., and Harris, A. P.: Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of  $11\beta$ -hydroxylation, *J. Clin. Endocrinol. and Metabolism* **18**: 906, 1958.
7. Jenkins, J. S., Meakin, J. W., Nelson, D. H., and Thorn, G. W.: Inhibition of adrenal steroid  $11$ -oxygenation in the dog, *Science* **128**: 478, 1958.
8. Frantz, A. G., Holub, D. A., and Jailer, J. W.: Further evidence of a relative lack of C-21 hydroxylation in congenital adrenal hyperplasia, *J. Clin. Investigation* **39**: 904, 1960.
9. Norymberski, J. K., and Stubbs, R. D.: Assessment of adrenocortical activity by assay of 17-ketogenic steroids in urine, *Lancet* **2**: 1276, 1953.
10. Sobel, C., Henry, R. J., Golub, O. J., and Rudy, M.: Chemical determination of aldosterone in urine, *J. Clin. Endocrinol. and Metabolism* **19**: 1302, 1959.
11. Ulick, S., Laragh, J. H., and Lieberman, S.: The isolation of a urinary metabolite of aldosterone and its use to measure the rate of secretion of aldosterone by the adrenal cortex in man, *Tr. A. Am. Physicians* **71**: 225, 1958.
12. Peterson, R. E.: Adrenocortical steroid metabolism and adrenal cortical function in liver disease, *J. Clin. Investigation* **39**: 320, 1960.
13. Yates, F. E., Urquhart, J., and Herbst, A. L.: Impairment of the enzymatic inactivation of adrenal cortical hormones following passive venous congestion of the liver, *Am. J. Physiol.* **194**: 65, 1958.
14. Wolff, H. P., Koczorek, Kh. R., and Buchborn, E.: Aldosterone and antidiuretic hormone (adiuretin) in liver disease, *Acta endocrinol.* **27**: 45, 1958.
15. Bartter, F. C.: Secondary aldosteronism, in *Clinical endocrinology*, I, E. B. Astwood, Editor, 1960, Grune and Stratton, New York.
16. Birkenfeld, L. W., Liebman, J., O'Meara, M. P., and Edelman, I. S.: Total exchangeable sodium, total exchangeable potassium, and total body water in edematous patients with cirrhosis of the liver and congestive heart failure, *J. Clin. Investigation* **37**: 687, 1958.
17. Perera, G. P.: The plasma volume in Laennec's cirrhosis of the liver, *Ann. Int. Med.* **24**: 643, 1946.
18. Davis, J. O., Goodkind, M. J., Pechet, M. M., and Ball, W. C., Jr.: Increased excretion of aldosterone in urine from dogs with right-sided congestive heart failure and from dogs with thoracic inferior vena cava constriction, *Am. J. Physiol.* **187**: 45, 1956.
19. Ross, E. J.: Aldosterone in clinical and experimental medicine, 1959, Charles C Thomas, Springfield, Ill., p. 108.
20. Marson, F. G. W.: Total adrenalectomy in hepatic cirrhosis with ascites: preliminary communication, *Lancet* **2**: 847, 1954.
21. Giuseffi, J., Werk, E. E., Jr., Larson, P. U., Schiff, L., and Elliott, D. W.: Effect of bilateral adrenalectomy in a patient with massive ascites and post-necrotic cirrhosis, *New England J. Med.* **257**: 796, 1957.
22. Baronofsky, I. D., Faucett, R. E., and Weiss, H. A.: Total adrenalectomy in the treatment of intractable ascites, *J. A. M. A.* **172**: 231, 1960.
23. Kerr, D. N. S., Read, A. E., Haslam, R. M., and Sherlock, S.: The use of a steroidal spiro lactone in the treatment of ascites in hepatic cirrhosis, *Lancet* **2**: 1084, 1958.
24. Liddle, G. W.: Aldosterone antagonists, *Arch. Int. Med.* **102**: 998, 1958.
25. Cejka, V., de Vries, L. A., and Borst, J. G. G.: The diuretic effect of spiro lactone SC-9420 in a case of secondary aldosteronism, *Lancet* **1**: 312, 1960.
26. Cloudus, B. F., Higgins, J. A., Rosevear, J. W., and Summerskill, W. H. J.: Treatment of "refractory" ascites with a new aldosterone antagonist in patients with cirrhosis, *Proc. Staff Meet., Mayo Clin.* **35**: 97, 1960.
27. Salassa, R. M., and Mattox, V. R.: Effects of a chemical inhibitor of  $11\beta$ -hydroxylation on the urinary steroid pattern in primary hyperaldosteronism, *J. Lab. and Clin. Med.* **54**: 940, 1959.

28. Coppage, W. S., Jr., Island, D., Smith, M., and Liddle, G. W.: Inhibition of aldosterone secretion and modification of electrolyte excretion in man by a chemical inhibitor of  $11\beta$ -hydroxylation, *J. Clin. Investigation* **38**: 2101, 1959.
29. Jenkins, J. S., Pothier, L., Reddy, W. J., Nelson, D. H., and Thorn, G. W.: Clinical experience with selective inhibition of adrenal function, *Brit. M. J.* **1**: 398, 1959.
30. Gold, E. M., DiRaimondo, V. C., and Forsham, P. H.: Quantitation of pituitary corticotropin reserve in man by use of an adrenocortical  $11$ -beta hydroxylase inhibitor (SU-4885), *Metabolism* **9**: 3, 1960.
31. Hudson, J. B., Chobanian, A. V., and Relman, A. S.: Hypoaldosteronism: a clinical study of a patient with an isolated adrenal mineralocorticoid deficiency, resulting in hyperkalemia and Stokes-Adams attacks, *New England J. Med.* **257**: 529, 1957.
32. Liddle, G. W.: Sodium diuresis induced by steroidal antagonists of aldosterone, *Science* **126**: 1016, 1957.
33. Vesin, P., Funel, P., Lemonnier, F., and Beaulieu, E. E.: Réduction de l'hyperaldostéronisme au cours d'une cirrhose ascitique sous l'action de la delta-cortisone, *Semaine d. hôp. Paris* **32**: 3205, 1956.
34. Stormont, J. M., Crabbe, J., Fast, B., Wolfe, S. J., and Davidson, C. S.: The effect of prednisone and amphenone on fluid and electrolyte balance and on aldosterone excretion of patients with cirrhosis and ascites, *J. Lab. and Clin. Med.* **53**: 396, 1959.
35. Carbone, J. V., and Matthews, H. B.: The use of prednisone to initiate or potentiate diuresis in chronic hepatic disease with ascites, *Gastroenterology* **38**: 52, 1960.

# CLINICAL MEASUREMENT OF GASTRIC SECRETION: SIGNIFICANCE AND LIMITATIONS\*†

By HARRY L. SEGAL, M.D., F.A.C.P., Rochester, N. Y.

## INTRODUCTION

A DECADE of experience with tubeless gastric analysis technics has provided sufficient data to allow a comparative evaluation of intubation and tubeless gastric analysis procedures in clinical medicine. This paper will describe the rationale, indications and limitations of a proposed gastric analysis routine, developed as a result of this evaluation.

In the past, clinical gastric analysis has concerned itself largely with the measurement of the hydrochloric acid and, to a lesser extent, with the level of enzyme activity in the gastric contents obtained by aspiration. The degree of acidity has been divided arbitrarily into hyperacidity, normal acidity, hypoacidity and achlorhydria, depending upon the hydrogen ion concentration (pH) of the aspirated juice. Hollander<sup>1</sup> has designated a concentration (table 1) of free hydrochloric acid greater than 50 mEq./L. (pH, > 1.3) as hyperacidity; that between 15 and 50 mEq./L. (pH, 1.8 to 1.3) as normal; and that between 1 and 15 mEq./L. (pH, 3.0 to 1.8) as hypoacidity; while that less than 1.0 mEq./L. (< pH 3.0) has been designated as achlorhydria.

TABLE 1  
Arbitrary Divisions of Gastric Acidity<sup>1</sup>

mEq./L.	Degree of Gastric Acidity	pH	Normality
100.00	Hyper	1.0	0.1
50.00		1.3	0.05
15.00	Normal	1.8	0.015
1.00	Low	3.0	0.001
0.0001	"Relative" Achlorhydria	7.0	0.0000001
0.0000032	True Achlorhydria	8.5	0.0000000032

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From the Departments of Medicine, the Genesee, Strong Memorial and Rochester Municipal Hospitals, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

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Requests for reprints should be addressed to Harry L. Segal, M.D., The University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 20, N. Y.

The term "achlorhydria" requires further clarification. In routine gastric analysis, achlorhydria has signified a range of hydrogen ion concentration from a pH of 3.0 to 8.2 without too much consideration of method, or type and dose of the gastric stimulant. This has resulted in a lack of clarity which has been exemplified by comparison of acidity measured by the tubeless method, with caffeine as gastric stimulant, with that by the intubation procedure, with histamine as the gastric stimulant.<sup>2,3</sup> The relative meaning of the term achlorhydria is further substantiated by the following facts: About 50% of individuals achlorhydric to caffeine stimulation by tubeless gastric analysis will secrete free hydrochloric acid with Histalog as the gastric stimulant.<sup>4</sup> Practically all individuals found achlorhydric after stimulation with the usual histamine doses, with the exception of patients with pernicious anemia or with comparable gastric atrophy, will secrete free hydrochloric acid after maximal histamine stimulation (Kay's augmented histamine test<sup>5</sup>). It is thus evident that the detection of true achlorhydria will depend upon the type and dose of the gastric stimulant. In the opinion of Shay et al.<sup>6</sup> true achlorhydria can be diagnosed only if, under proper conditions, the pH is 8.2 or greater. On the other hand, James<sup>7</sup> has implied that complete achlorhydria is present if, during fractional aspiration, the pH fails to fall to the neighborhood of 3.0 from a significantly higher level, such as a pH of 6.0 or 7.0.

The term "achylia" likewise requires elucidation. Although, in the pure sense, achylia designates the lack of all gastric secretory elements, it is frequently used to denote the absence of only two of the gastric secretory substances, i.e., free hydrochloric acid and pepsinogen.

#### SIGNIFICANCE OF GASTRIC ANALYSIS

There are definitive clinical indications to determine the gastric hydrochloric acid secretory status as achlorhydria, achylia and the degree of gastric acidity or the hydrochloric acid output per unit of time.

*Significance of Achlorhydria:* The detection of *relative* achlorhydria may be significant in:

1. The early detection of carcinoma of the stomach.
2. The follow-up of a patient with a gastric ulcer niche.
3. Diagnosis and therapy of some functional digestive disturbances.
4. Ruling out the diagnoses of duodenal ulcer in a patient with a pseudo-ulcer syndrome.
5. Evaluating the completeness of vagotomy.

The detection of *true* achlorhydria or achylia is significant in:

1. The diagnosis of pernicious anemia.
2. The decision for immediate surgery in a patient with a gastric ulcer niche.
3. The early detection of gastric carcinoma.

The incidence of gastric carcinoma has been reported to be three and 10 times greater in achlorhydric and achylic individuals, respectively, than in acid secretors of comparable ages.<sup>10</sup> The early detection of gastric carcinoma may be enhanced by screening individuals over 40 or 50 years of age for achlorhydria or achylia for further appropriate investigations. This approach should be of increased significance in subjects with a family history of pernicious anemia or gastric carcinoma.<sup>11,12</sup> The knowledge that achlorhydria or achylia is present in an individual with symptoms suggestive of carcinoma but without definitive objective evidence may be decisive for surgical exploration.

The knowledge of the presence of relative or true achlorhydria is of value in following a patient with a gastric ulcer niche. Relative achlorhydria alone does not necessarily signify that the gastric ulcer niche is malignant. A gastric juice with a pH between 3 and 4 may have considerable proteolytic enzyme activity due to cathepsin.<sup>8,9</sup> This type of achlorhydria in a patient with a gastric ulcer niche is usually temporary, and may be on the basis of gastritis associated with the gastric ulcer. In such circumstances, free hydrochloric acid secretion will return with the healing of the ulcer. On the other hand, the persistence of relative achlorhydria, the presence of true achlorhydria or achylia, or the disappearance of free gastric hydrochloric acid previously present in a patient with a gastric ulcer niche should be an indication for surgery, regardless of the appearance or apparent healing of the niche by roentgen examination.

*Significance of Quantitative Determination of Acidity:* The measurement of the degree of acidity or the hydrochloric acid output during a specific period may occasionally be significant in the diagnosis of duodenal ulcer, in evaluating the type of surgery in the case of a duodenal ulcer, or in determining the completeness of vagotomy.

#### PROCEDURES TO MEASURE GASTRIC SECRETORY ACTIVITY

The availability of tubeless procedures to measure gastric acidity and gastric pepsinogen secretion makes it appropriate to correlate the information so obtained with that provided by intubation techniques in order to learn their relative value in the clinical measurement of gastric secretory activity.

#### TUBELESS GASTRIC ANALYSIS

A brief description of the gastric secreting cells might help in the appreciation of the rationale of the tubeless technics. The types of cells in the glandular tubules of the gastric mucosa consist of mucus-secreting, acid-secreting parietal cells and proteolytic enzyme-secreting chief cells, all of which vary in number in the various anatomic divisions throughout the stomach. It is these cells, plus other factors, which directly and indirectly secrete the substances that form the complex mixture known as gastric juice.

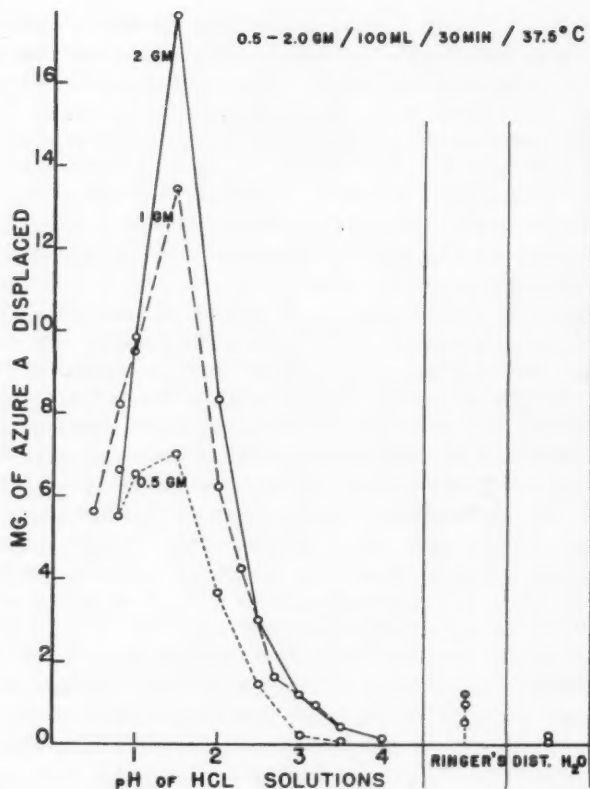


FIG. 1. Elution of azure A from varying quantities of azure A resin compound. (From Segal et al.,<sup>16</sup> reproduced with permission of *Gastroenterology*.)

Although the secretory products of these cells pass mainly into the stomach cavity, there is a small but significant passage of enzymes from the chief cells directly into the blood, with eventual excretion in the urine.<sup>13, 14</sup>

*Tubeless Analysis for Gastric Hydrochloric Acid:* Tubeless gastric analysis with ion exchange compounds, introduced in 1950 by Segal et al.<sup>15</sup> has been further simplified by the development of the azure A resin compound.<sup>16</sup> The ability to measure the presence or absence of free gastric hydrochloric acid by tubeless gastric analysis with the latter resin compound\* depends upon the displacement of the azure A dye from the azure A resin compound by the hydrogen ions (pH) available in the gastric juice (figure 1). The mere visual appraisal of the color change in the urine resulting from this displacement determines whether the pH of the gastric juice is below or above 3.

\* Commercially available as Diagnex Blue (E. R. Squibb and Sons).



## PROCEDURE FOR TUBELESS GASTRIC ANALYSIS WITH DIAGNEX BLUE

*Instructions for the Patient*

1. The patient eats no breakfast until the test is completed. (Water may be taken as desired.)
2. The first urine passed on arising is discarded.
3. The gastric stimulant is taken with one glass of water. Either two tablets, each containing 250 mg. caffeine sodium benzoate, or a capsule containing 50 mg. of Histalog, can be used as the oral gastric stimulant. Histalog or histamine can also be administered subcutaneously as the gastric stimulant.
4. The blue granules mixed in one-half glass of water are swallowed one hour after the gastric stimulant.
5. The patient urinates two hours after ingesting the granules and saves the entire quantity.

*Examination of the Urine*

1. If the total urine collection is less than 300 ml., it is diluted with water to 300 ml.\*
2. Ten milliliter aliquots of this urine are poured into each of two test tubes and the color is noted.† To each aliquot, one drop of a solution containing 195 mg.  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  in 100 ml. of 18% HCl (6M)‡ is added. (If crystallized copper sulfate is unavailable, one drop of a solution made by mixing 40 ml. of water and 10 ml. of Benedict's solution with 50 ml. of concentrated hydrochloric acid may be used.)
3. The test tubes are placed in a boiling water bath for 10 minutes and then cooled at room temperature for two hours.† A pinch of L-ascorbic acid<sup>18</sup> (about 300 mg.) is added to one of the urine aliquots. (This reduces the dye to a colorless form which allows this sample to be used as the control urine.)
4. The color of both aliquots of urine is compared with the standards.§ If the color is less than the 0.6-mg. standard, the volume of the total urine collection, if greater than 300 ml., must be taken into consideration. Example: If the total volume of the urine collection is 600 ml., and the color of the aliquot equals the 0.3 mg./300 ml. standard, calculation is made as follows:

$$\frac{(\text{Vol. of Urine}) \times (\text{Mg. of Azure A})}{300 \text{ ml.}} = \text{Total Mg. Azure A Excreted}$$

$$\frac{600 \times 0.3}{300} = 0.6 \text{ Mg. Azure A}$$

*Interpretation of Standards*

Mg. Azure A in Urine Collection		Status of Gastric Acid Secretion
0.6 or >	signifies	Free Gastric HCl
< 0.35	signifies	No Free Gastric HCl
0.35 to 0.6	signifies	Borderline Secretion

\* An aliquot of this diluted urine can be used to determine the uropepsin activity.

† If at any time the color of the urine indicates the secretion of free acid, no further treatment is necessary. The intensity of color that denotes free acid secretion will be easily recognized with a little experience.

‡ This solution is marketed as Diagnex Reagent (Squibb).

§ A simple comparator block with standards is provided by E. R. Squibb and Sons with the Diagnex Blue packets.

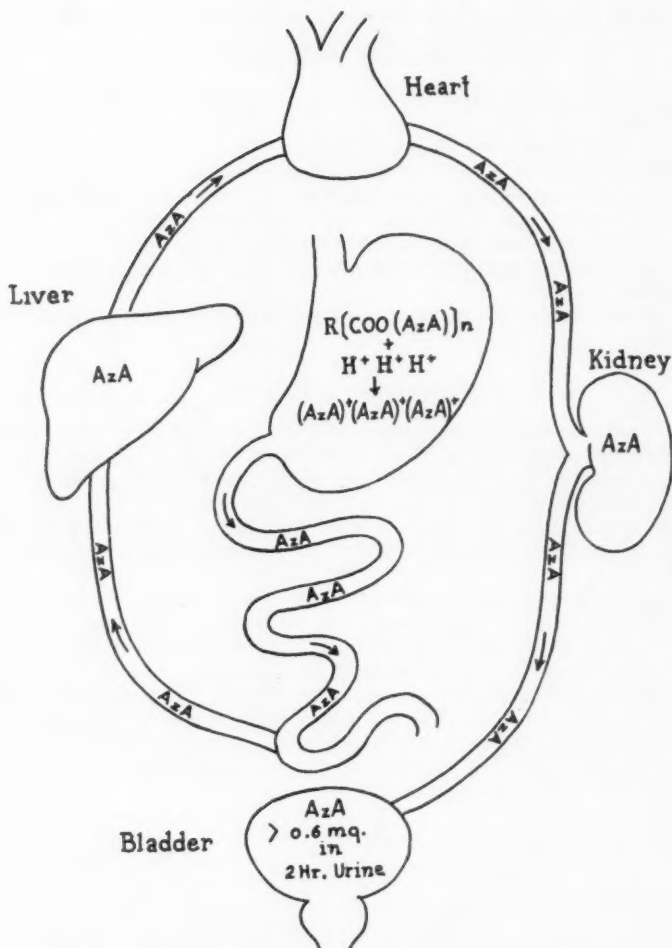


FIG. 2. Illustration of rationale to detect free gastric hydrochloric acid by tubeless gastric analysis with the azure A resin compound.

It is obvious that certain conditions (figure 2) will interfere with the chain of events necessary for proper interpretation, namely, vomiting, pyloric obstruction, malabsorption, severe dysfunction of the liver or kidney, or urinary retention.\* Tubeless gastric analysis is also not reliable in a patient with a subtotal gastrectomy, gastroenterostomy or pyloroplasty. A

\*The measurement of the blood azure A level<sup>17</sup> can be substituted for that of the urinary azure A level in patients in whom the urine collection may be unreliable.

repeat test with Diagnex Blue requires an interval of four to five days because of the delayed excretion of the azure A dye.

*Tubeless Technics for Measuring Gastric Pepsinogen Activity:* The indirect estimation of gastric pepsinogen secretion by the quantitative measurement of the blood or urinary pepsin activity is much more complicated than the tubeless test for determining gastric acidity. The method employed for the determination of blood plasma pepsinogen is that of I. A. Mirsky's modification<sup>19</sup> of Anson and Mirsky's procedure,<sup>20</sup> in which hemoglobin is used as the substrate. The methods commonly employed for measuring uropepsin activity are based either on various modifications of the Anson-Mirsky procedure, or on the Sylvest milk-clotting technic<sup>21</sup> as modified by West et al.<sup>22</sup>

Although the mean activity of blood pepsin and uropepsin is high in duodenal ulcer individuals, low, normal or elevated in individuals with gastric ulcer, low in those with gastric cancer, and extremely low or absent in pernicious anemia patients, a single determination in any one individual is not of critical diagnostic value.<sup>23</sup> However, the consistent absence of uropepsin activity in more than one urine collection may be significant in the diagnosis of pernicious anemia or of gastric cancer, and in suspecting malignancy in a patient with a gastric ulcer niche. It is for the latter reasons that the determination merely of the presence or absence of uropepsin activity by any simple test would be of more practical value than would quantitative measurement.

At this time, attention must be drawn to the fact that the absence of uropepsin activity as measured by the acid hemoglobin technic<sup>23</sup> does not necessarily indicate the inability of the stomach to secrete acid. Because of this, studies are now in progress to learn whether the absence of uropepsin as measured by a modified West technic developed by Segal and Miller<sup>24</sup> will be a consistent indicator of the absence of free gastric hydrochloric acid and/or gastric pepsinogen secretion.

It is also important to note that the presence of uropepsin activity as measured by the acid hemoglobin method does not always signify the secretion of either hydrochloric acid or pepsinogen into the stomach cavity.<sup>23</sup> The absence of free hydrochloric acid in an individual with urinary pepsin activity may be significant in the diagnosis of gastritis.

#### MODIFIED WEST TECHNIC<sup>24</sup>

The purpose of this modification is to provide a simple means of determining merely the presence or absence of uropepsin activity.

The test is performed as follows:

1. The three-hour urine dilution employed for measuring the amount of azure A in the urine is used for this purpose. (The result may be unreliable if the pH of the undiluted urine is greater than 8.0.)
2. One-tenth milliliter of 2 N HCl is added to 2 ml. of urine. The acidified urine is incubated for one hour in a water bath (37.5° C.) to activate the pepsin.

3. At the end of the one-hour period, the following solutions are added to 0.1 ml. of this activated urine:
  - 0.9 ml. distilled water
  - 1.0 ml. acetate buffer, pH 4.9 (4.2 gm. NaOH; 9.2 ml. glacial acetic acid; distilled water to make 100 ml.)
4. To start the reaction, 0.5 ml. of a mixture of equal parts of fresh homogenized milk and acetate buffer (pH 4.9) is added to this solution, which is then incubated at 37.5° C. for 20 minutes.
5. The test tube is then shaken and inspected for aggregation of casein particles (i.e., coagulation). If coagulation is now present, the test indicates the presence of uropepsin activity. The test is completed.
6. If no coagulation is present at the 20-minute reading, the milk-buffer mixture is allowed to remain incubated for another 20 minutes. The lack of coagulation at or after this 40-minute period of incubation indicates the absence of uropeptic activity. Coagulation at this time should be interpreted as an equivocal result. In the latter case, the test should be repeated.

#### INTUBATION TECHNICS

The measurement of the acidity of the gastric contents obtained by intubation should have as its primary purpose the estimation of the active parietal cell mass. The most logical means to accomplish this would necessitate maximal stimulation and continuous aspiration. The Kay augmented histamine test<sup>5</sup> seems to fulfill these requirements.

#### KAY'S AUGMENTED HISTAMINE TEST

1. The test is preceded by a 12-hour fast.
  2. A nasogastric tube is introduced into the stomach, and the fasting juice is aspirated and discarded.
- A. To measure both basal secretion and maximal parietal cell activity, proceed as follows:
1. The basal gastric secretion is continuously collected for a period of 45 minutes. The total volume collected during this period is measured, and its free and total hydrochloric acid outputs are determined in the usual manner, and expressed in either milliequivalents or milligrams.
  2. One hundred milligrams of mepyramine hydrogen maleate (Neo-Antergan) are injected intramuscularly.
  3. The gastric juice is aspirated for the next 30 minutes and discarded.
  4. Histamine acid phosphate (0.04 mg. per kilogram of body weight) is then injected subcutaneously.
  5. The histamine-provoked secretion is continuously aspirated. The volume secreted in the half-hour period from 15 to 45 minutes after the histamine injection is measured and its titratable free and total hydrochloric acid outputs are determined. The free and total hydrochloric acid outputs during this 30-minute interval are expressed in milliequivalents or milligrams, and represent the maximal parietal cell response.
- B. To measure maximal secretory activity without basal secretion:
1. Omit Step 1, and proceed directly to Steps 2, 3, 4 and 5 under "A".

This test has been found to be significant in the diagnosis of duodenal ulcer when the 30-minute free hydrochloric acid output obtained after stimulation with 0.04 mg. of histamine acid phosphate was greater than 33 mEq. (1,200 mg.) (table 2). However, this level occurred in only 19% of the duodenal ulcer patients tested. Marks and Shay<sup>26</sup> have found that the measurement of the acidity of gastric aspirates collected at 15-minute intervals for a period of two hours following the Ewald meal (two pieces of zwieback and 350 ml. water) was generally as informative as the augmented histamine test in supporting a diagnosis of duodenal ulcer. Since the augmented histamine test not only is well tolerated by the vast majority of patients,<sup>5, 26</sup> but also requires a much shorter period of time than the Ewald fractional test, it would appear to be the intubation test of choice to aid in the diagnosis of duodenal ulcer.

The knowledge of the 45- or 60-minute basal hydrochloric acid output may also aid in the diagnosis of duodenal ulcer. In Kay's series<sup>5</sup> it was of diagnostic aid in 10% of his duodenal ulcer patients. Kirsner and Ford<sup>27</sup> and Levin et al.<sup>28</sup> reported a much higher average one-hour basal secretory output in duodenal ulcer patients than in gastric ulcer patients or in normals. However, the significance of the one-hour basal hydrochloric acid output in a single individual cannot be stated, because the upper limit of the basal hydrochloric acid output in their normals was not given in their reports.

TABLE 2  
Frequency Distribution of Maximum Acid Output (Males)  
(Adapted from Kay<sup>5</sup>)

Basal Secretion					After Stimulation				
Free HCl Output					Free HCl Output				
mg.	%	%	%	mEq.	mg.	%	%	%	mEq.
2,000									55.0
1,800					3				49.5
1,600					3				44.0
1,400					5				38.5
1,200					8				33.0
1,000					16	5	5		27.5
800	5			27.5	18	10	7		22.0
600	5			22.0	18	15	12		16.5
400	15	5		16.5	17	30	28		11.0
200	20	10	5	11.0	7	15	20		5.5
0	55	85	95	5.5	5	25	28		0.0
	D.U.	G.U.	N	0.0		D.U.	G.U.	N	

D.U.—Duodenal Ulcer  
G.U.—Gastric Ulcer  
N—Normal

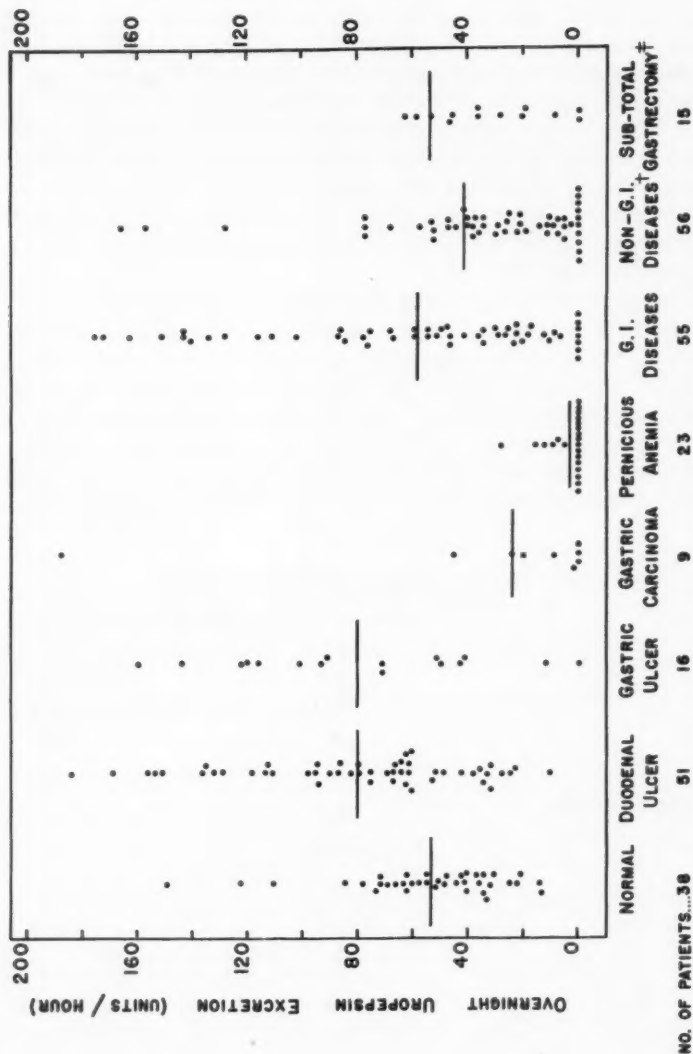


Fig. 3. Average uropeptic activity in various clinical states. (From Segal et al.,<sup>28</sup> reproduced with permission of *Gastroenterology*.)

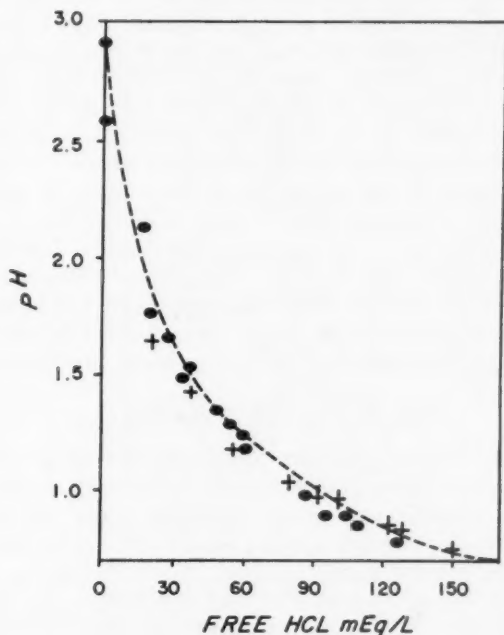


It is possible that the measurement of the basal gastric hydrochloric acid output may suggest the advisability of additional vagotomy in a patient to be subjected to subtotal gastrectomy.

The insulin intubation technic is the only means that might help in evaluating the completeness of vagotomy.

The tubeless quantitative determination of uropepsin activity is not usually diagnostic in the individual patient, due to the frequency of overlapping of the level of uropepsin activity in patients with duodenal ulcer, gastric ulcer, gastric carcinoma and normals (figure 3).

*Choice of Method to Measure Acidity of Gastric Contents:* A brief description of the method of measuring acidity of the gastric samples obtained by aspiration seems pertinent. Hollander<sup>29</sup> has suggested that the determination of the pH of gastric contents obtained by intubation should provide, in the low acid range, an indirect means of estimating the milliequivalents



BROKEN LINE REPRESENTS THEORETICAL RELATION.  
THE DOTS REPRESENT GASTRIC CONTENTS. THE  
CROSSES REPRESENT AQUEOUS SOLUTIONS OF HCL.

FIG. 4. Relation between pH measured electrometrically and hydrogen ion concentration determined by titration. (From James and Pickering,<sup>30</sup> reproduced with permission of *Clinical Science*.)

of hydrochloric acid per liter and/or per volume of gastric juice per unit of time. Figure 4, taken from James and Pickering,<sup>30</sup> shows the theoretic relation between pH and hydrogen ion concentration at 25° C. in aqueous solutions of hydrochloric acid. To learn whether this relation applies to gastric samples, James and Pickering<sup>30</sup> compared the pH obtained by electrometric method with the acidity procured by titration of gastric samples and aqueous solutions of hydrochloric acid. The agreement between experiment and theory was reasonably close. From table 1 it is apparent that a small change in pH at high acidity represents a large difference in hydrogen ion concentration, while a comparable change at lower acidity depicts insignificant variation in hydrogen ion concentration. To be more exact, a change in pH of 0.1 unit represents about 26 mN (26 mEq./L.) at pH 1.0. In the lower levels, such as at pH 2.0, a comparable change in pH of 0.1 unit represents 3.5 mN (3.5 mEq./L.). This suggests that pH test paper might be substituted for titration of gastric juice only in the lower acid range.

Sippy and Fitzsimons<sup>31</sup> have recommended the use of Hydrion test paper (pH 1-6) instead of titration for measuring the degree of gastric acidity. An examination of one of their tables shows a difference of 0.4 pH unit between the glass electrode meter reading at pH 1.4 and the Hydrion test paper (pH 1-6) reading at pH 1.0. The additional error in the high acidity range between hydrogen ion concentration and the pH electrometric reading would compound the inaccuracy in this range. It would appear from this that the pH test paper would be of value only in estimating the approximate gastric acidity or the free hydrochloric acid output in the lower acid range (pH 1.8-3.0). The narrow range pH test papers now available would seem to be more suitable than a test paper with a pH range of 1-6. The use of pH test papers might also be advantageous in measuring the approximate acidity of therapeutic aspirations and/or that of vomitus.

#### ROUTINE GASTRIC ANALYSIS

The evaluation of the significance and limitations of the tubeless and intubation technics has allowed the design of the following routine approach (figure 5) in the examination of gastric secretory activity for clinical purposes. The presence or absence of free gastric hydrochloric acid should be determined first by tubeless gastric analysis, unless contraindicated by one of the conditions previously described. With this technic, the choice of the gastric stimulant will depend upon the clinical problem. Caffeine sodium benzoate is probably the oral stimulant of choice for mass screening, or to evaluate the presence or absence of hydrochloric acid associated with digestion. Orally administered Histalog\* is preferable to caffeine as the gastric stimulant to select individuals for further studies to detect true achlorhydria and/or achylia.<sup>32</sup>

\* Fifty-milligram capsules of Histalog were supplied through the courtesy of Dr. James Hammond, Eli Lilly and Company.

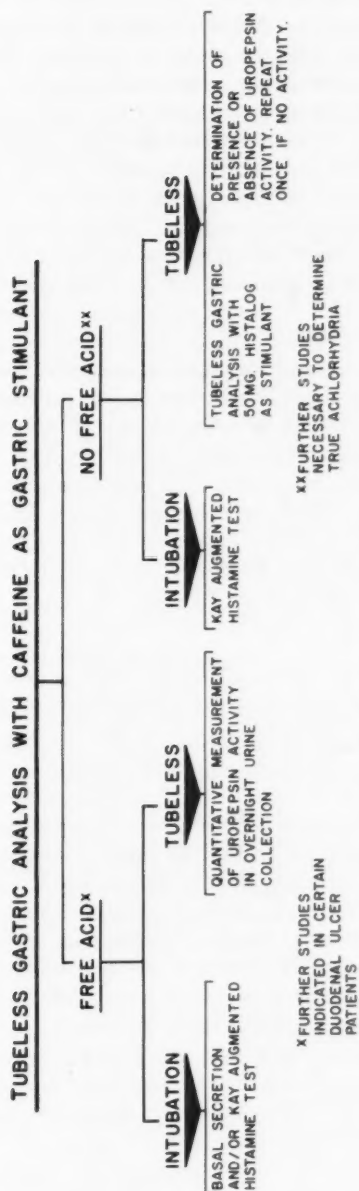


Fig. 5. Guide for routine gastric analysis.

If achlorhydria is noted by tubeless gastric analysis, with either caffeine or Histalog as the oral gastric stimulant, further investigation is necessary to establish a true achlorhydria or achylia. Although the Kay augmented histamine intubation technic is the most reliable means to detect complete achlorhydria, studies in progress suggest that true achlorhydria and/or achylia may be detected, or at least eliminated as a possibility, without intubation. The absence of free acid by tubeless gastric analysis with Histalog as the gastric stimulant combined with the absence of uropepsin activity, as measured by the modified West technic,<sup>23</sup> may be presumptive evidence of true achlorhydria or achylia.<sup>24</sup> On the other hand, the presence of uropepsin activity by this technic may definitely rule out true achlorhydria or achylia.

If the proper application of the tubeless gastric analysis technic signifies the presence of free hydrochloric acid, intubation gastric analysis will usually be of little significance. As already stated, the determination of the basal gastric secretory pattern or of the hydrochloric acid output after maximal histamine stimulation<sup>5</sup> may be of some value in the diagnosis of duodenal ulcer. Although the quantitative appraisal of blood or urinary pepsin activity is usually of limited significance,<sup>25</sup> it may provide additive evidence to help in the differentiation between a benign and a malignant lesion of the stomach. The quantitative measurement of blood pepsin activity has been shown to be valuable in mass screening of individuals who may have a propensity to develop duodenal ulcer.<sup>33</sup>

#### SUMMARY

The rationale, indications and limitations of a proposed system for clinical measurement of gastric secretory activity have been described.

The following routine has been suggested for measuring gastric secretory activity:

Unless contraindications exist, the presence or absence of free hydrochloric acid should be determined first by tubeless gastric analysis. If this procedure signifies the secretion of free gastric hydrochloric acid, there is very little reason for subjecting an individual to intubation except in the occasional patient in whom the diagnosis of duodenal ulcer is equivocal. In such a patient, the measurement of the hydrochloric acid output of the gastric contents aspirated during a basal period or after stimulation with a maximal dose of histamine may be of diagnostic significance.

If the tubeless gastric analysis denotes achlorhydria, further investigation is indicated, mainly to establish the diagnosis of a true achlorhydria or achylia. The presence of uropepsin activity when measured by a simplified modification of the West procedure will eliminate the diagnosis of true achlorhydria or achylia. The combination of no uropepsin activity by the modified West technic and no hydrochloric acid secretion by tubeless gastric analysis with orally administered Histalog as the gastric stimulant may be

presumptive evidence of achylia. The Kay augmented intubation technic seems at present to be the most reliable test to detect complete achlorhydria.

The value and limitations of the substitution of pH indicator test paper for titration of gastric juice obtained by aspiration have been described. A narrow range pH testing paper may be a practical substitute for titration to measure the hydrogen ion concentration in the lower acid range.

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#### SUMMARIO IN INTERLINGUA

Iste reporto describe un nove routine pro le mesuration clinic del activitate secretori del stomacho.

Le routine hic proponite es le sequente: Excepte in caso de contraindication, le presentia o absentia de libere acido hydrochloric debe primo esser determinate per analyse gastric sin tubo con le composito de resina azuro A (Blau Diagnex). Si iste manovra revela le secretion de libere acido hydrochloric gastric, il ha pauc ration pro subjicer le subjecto al intubation, excepte in le caso del patiente exceptional in qui le diagnose de ulcere duodenal es equivoc. In le patiente de iste genere, le mesuration del rendimento de acido hydrochloric in le contento gastric que ha essite aspirate durante un periodo basal o post le stimulation con un dose maximal de histamina es possiblemente de signification diagnostic. Le dose maximal de histamina subcutanee, secundo Kay, es 0,04 mg de diphosphato de histamina per kg de peso corporee (coperite per un agente antihistaminic).

Si le analyse gastric sin tubo reflecte achlorhydria, investigationes additional es indicate, principalmente pro establir le diagnose de un ver achlorhydria o achylia. Le presentia de activitate de uropepsina elimina possiblemente le diagnose de ver achlorhydria o achylia. Iste determination pote esser effectuate per medio de un simplicate modification del methodo de West (le qual es describite). Le combination del constatacion de nulle activitate de uropepsina per medio del modificate methodo de West e del constatacion de nulle secretion de acido hydrochloric per analyse gastric sin tubo con le administration oral de Histalog como stimulant gastric se trova currentemente sub investigation con le objectivo de verificar si o non illo pote fornir un indicio presumptive de achylia. Al tempore presente, le technica del intubation augmentate de Kay es le test le plus fidel pro le detection de achlorhydria complete.

Es proponite que al nivellos plus tosto basse de acido, un appropriate papiro de test pro pH va possiblemente provar se practic como substituto pro le titration.

#### BIBLIOGRAPHY

1. Hollander, F.: What is pH?, *Gastroenterology* 4: 497 (June) 1945.
2. Spiro, H. M., Poliner, I. J., and Hayes, M. A.: Detection of achlorhydria by indirect gastric analysis, *New England J. Med.* 256: 1051 (May 30) 1957.
3. Denborough, M. A., Retiff, F. P., and Witts, L. J.: Tubeless gastric analysis, *Brit. M. J.* 1: 1213-1215 (May 24) 1958.
4. Segal, H. L., Rumbold, J. C., Friedman, B. L., and Finigan, M. M.: Detection of achlorhydria by tubeless gastric analysis with betazole hydrochloride as the gastric stimulant, *New England J. Med.* 216: 544-546 (Sept. 10) 1959.

5. Kay, A. W.: Effect of large doses of histamine on gastric secretion of HCl. An augmented histamine test, *Brit. M. J.* **2**: 77-80 (July 11) 1953.
6. Shay, H., Komarov, S. A., and Berk, J. E.: Some fallacies in the clinical measurement of gastric acidity with special reference to the histamine test, *Gastroenterology* **15**: 110-117 (May) 1950.
7. James, A. H.: The physiology of gastric digestion, 1957, Edward Arnold, Ltd., London, p. 35.
8. Buchs, S.: Fundamental observations on the existence, extraction and activation of gastric cathepsin, *Enzymologia* **16**: 193, 1953.
9. Merten, R., Schramm, G., Grassmann, W., and Hannig, K.: Untersuchungen zur Reindarstellung des Magenkathepsins, *Ztschr. f. physiol. Chem.* **289**: 173, 1952.
10. Rigler, L. G., and Kaplan, H. S.: Pernicious anemia and tumors of the stomach, *J. Nat. Cancer Inst.* **7**: 327, 1947.
11. Videbaek, A., and Mosbech, J.: Genetic causal factors in cancer of the stomach, *Danish M. Bull.* **1**: 189, 1954.
12. Mackin, M. T.: The role of heredity in gastric and intestinal cancer, *Gastroenterology* **29**: 507, 1955.
13. Janowitz, H. D., and Hollander, F.: The exocrine-endocrine partition of enzymes in the digestive tract, *Gastroenterology* **17**: 591, 1951.
14. Hirschowitz, B. I.: Pepsinogen: its origins, secretion and excretion, *Physiol. Rev.* **37**: 475-511 (Oct.) 1957.
15. Segal, H. L., Miller, L. L., and Morton, J. J.: Determination of gastric acidity without intubation by use of cation exchange indicator compounds, *Proc. Soc. Exper. Biol. and Med.* **74**: 218-220, 1950.
16. Segal, H. L., Miller, L. L., and Plumb, E. J.: Tubeless gastric analysis with an azure A ion exchange compound, *Gastroenterology* **28**: 402-408 (Mar.) 1955.
17. Segal, H. L., Plosscowe, R. P., Gerle, R. D., and Russell, P. K.: The blood serum azure A level in the determination of gastric acidity by tubeless gastric analysis, *J. Lab. and Clin. Med.* **55**: 815 (May) 1960.
18. Rosenthal, H. L., and Buscaglia, S.: Tubeless gastric analysis, *J. A. M. A.* **168**: 409 (Sept. 27) 1958.
19. Mirsky, I. A., Futterman, P., Kaplan, S., and Broh-Kahn, R. H.: Blood plasma pepsinogen. The source, properties and assay of the proteolytic activity of plasma at acid reactions, *J. Lab. and Clin. Med.* **40**: 17 (July) 1952.
20. Anson, M. L., and Mirsky, A. E.: The estimation of pepsin with hemoglobin, *J. Gen. Physiol.* **16**: 59, 1932.
21. Sylvest, O.: The method for determining the renninogen of urine, *Acta med. scandinav.* **133**: 289, 1949.
22. West, P. M., Ellis, F. W., and Scott, B. L.: A simplified method for determining the excretion rate of uropepsin, *J. Lab. and Clin. Med.* **39**: 159-162 (Jan.) 1952.
23. Segal, H. L., Miller, L. L., Reichsman, F., Plumb, E. J., and Glaser, G. L.: Proteolytic enzyme activity. I. Urinary proteolytic activity at pH 1.5 in adults, *Gastroenterology* **33**: 557-565 (Oct.) 1957.
24. Segal, H. L., and Miller, L. L., in preparation for publication.
25. Spiro, H. M., and Schwartz, R. D.: Superficial gastritis. A cause of temporary achlorhydria and hyperpepsinemia, *New England J. Med.* **259**: 682 (Oct. 2) 1958.
26. Marks, I. N., and Shay, H.: Augmented histamine test, Ewald test meal and Diagnex test, *Am. J. Digest. Dis.* **5**: 1-23 (Jan.) 1960.
27. Kirsner, J. B., and Ford, H.: The gastric secretory response to Histalog: one-hour basal and Histalog secretion in normal persons and in patients with duodenal and gastric ulcer, *J. Lab. and Clin. Med.* **46**: 307-311, 1955.



28. Levin, E., Kirsner, J. B., and Palmer, W. L.: A simple measure of gastric secretion in man—comparison of one hour basal secretion, histamine secretion and twelve hour nocturnal gastric secretion, *Gastroenterology* **19**: 88-89 (Sept.) 1951.
29. Hollander, F.: Studies in gastric secretion. II. A comparison of criteria of acidity used in this investigation, *J. Biol. Chem.* **91**: 481-492, 1931.
30. James, A. H., and Pickering, G. W.: The role of gastric acidity in the pathogenesis of peptic ulcer, *Clin. Sc.* **8**: 181-210, 1949.
31. Sippy, H. I., and Fitzsimons, E. J.: Measurement of free acid in gastric juice by means of indicator paper, *J. A. M. A.* **170**: 1157-1158 (July 4) 1959.
32. Segal, H. L., Shepardson, C. R., and Plain, G. L.: Gastric hydrochloric acid secretory response to orally administered betazole hydrochloride, *New England J. Med.* **261**: 542-544 (Sept. 10) 1959.
33. Weiner, H., Thaler, M., Reiser, M. F., and Mirsky, I. A.: Etiology of duodenal ulcer. I. Relation of specific psychological characteristics to rate of gastric secretion (serum pepsinogen), *Psychom. Med.* **19**: 1 (Jan.-Feb.) 1957.

## EVALUATION OF A CHOLESTEROL-SYNTHESIS INHIBITOR (TRIPARANOL) \*

By MICHAEL J. CARVER, Ph.D.,† JOHN G. FREEMAN, M.D.,† *Omaha, Nebraska*, and JACKSON A. SMITH, M.D., F.A.C.P.,‡ *Chicago, Illinois*

THE role of cholesterol in the etiology and pathogenesis of atherosclerosis is not clearly understood; nevertheless, an association between hypercholesterolemia and atherosclerosis most probably exists, and has prompted continual study of methods of decreasing the level of serum cholesterol.

The findings of Blohm et al. that Triparanol § produced a cholesterol-lowering effect on rats, and that the effect was the result of an inhibition of cholesterol biosynthesis, were met with interest by investigators. It was further established by Blohm et al. that the inhibition noted was specific for cholesterol.<sup>2</sup> Avigan et al.<sup>1</sup> indicate that the principal site of action of Triparanol is at the last step in the biosynthesis of cholesterol, that is, in the reduction of the side chain double bond of 24-dehydrocholesterol.

In view of the results obtained in animals, it was considered important to evaluate Triparanol for its effect on the level of serum cholesterol in humans. Several such experiments<sup>3,4</sup> have been reported; however, the period of treatment was short (four weeks), and no follow-up was indicated. The present study is a report of the findings obtained in a study of the cholesterol-inhibitor preparation over an extended interval of time at different dosages. The early part of this study and other short-term studies substantiate the effects noted by previous workers, but the later part of this study seems to indicate that continued administration of this preparation does not maintain the lowered level of serum cholesterol observed in the short-term experiments.

### MATERIAL AND METHODS

Twenty-nine patients participated in the beginning of the study. Levels of serum cholesterol were determined (in duplicate, with agreement within 5 mg.%) by the method of Zak et al.<sup>7</sup> Base line determinations of levels of

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† From the Nebraska Psychiatric Institute and the University of Nebraska College of Medicine, Omaha, Nebraska.

‡ Formerly of Nebraska Psychiatric Institute; now of Illinois State Psychiatric Institute, Chicago, Illinois.

§ 1-[p-( $\beta$ -diethylaminoethoxy)-phenyl]-1-(p-tolyl)-2-(p-chlorophenyl) ethanol. Triparanol used in this study was supplied as MER-29 by Wm. S. Merrell Company.

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Requests for reprints should be addressed to Michael J. Carver, M.D., Nebraska Psychiatric Institute, The University of Nebraska College of Medicine, 602 South Forty-fourth Avenue, Omaha 5, Nebraska.

serum cholesterol were obtained one week apart in Group I; four base line determinations at weekly intervals were made in Group II. Group I, consisting of 11 patients, was subdivided into Group I-A, of six patients, and Group I-B, of five patients. Group II consisted of 18 patients.

*Group I-A:* Six patients (average age, 58.8 years) were given Triparanol, 750 mg. daily. After two weeks, two patients were dropped from the study because they developed a mild rash; somewhat later, despite a return of the rash, they were given 250 mg. daily for eight weeks. Four patients completed the original study of six weeks of medication.

*Group I-B:* Five patients were given Triparanol, 250 mg. daily. After 46 weeks, four patients (average age, 52.8 years) are still participating in the study. One patient was eliminated because several determinations of levels of serum cholesterol were missing, and because medication was discontinued during the twenty-seventh week because of a low white blood cell count; medication was started again during the thirtieth week, but again

TABLE 1  
Changes in Total Cholesterol: Group I-A

Subject	Duration of Treatment	Mean of 2 Initial Total Cholesterols (mg./100 ml. serum)	Average % Change from Initial Mean	Lowest Level during Treatment (mg./100 ml. serum)
A. C.	6 weeks	272	-17.3	202
H. T.	6 weeks	308	-22.9	220
A. W.	6 weeks	279	-10.0	232
I. W.	6 weeks	254	-12.0	206
E. H.	2 weeks	247	-10.1	216
M. O.	2 weeks	250	6.0	244

Triparanol dosage: 750 mg. daily for indicated time.

discontinued in the thirty-fourth week because of a low white blood cell count. The other four patients received the medication at a dosage of 250 mg. daily for six weeks; no medication was given for the next 15 weeks; at the beginning of the twenty-first week the dose of 250 mg. daily was resumed and has been continued to the present time, which is the forty-eighth week.

*Group II:* This group consisted of 18 patients. One patient (for psychiatric reasons) refused food and medication; the remaining 17 patients were followed for six weeks at a dosage level of 125 mg. daily. Ten of these patients (average age, 36.1 years) continued to be followed, first for 21 weeks at 125 mg. daily, and subsequently at a doubled dosage (250 mg.) daily to the present time, which is the thirty-eighth week.

## RESULTS

The results obtained in Group I-A are presented in table 1. At a dosage level of 750 mg. daily there is a sharp drop in the level of serum cholesterol

during the first week of therapy. During the six weeks of therapy, the initial drop is not maintained. As tabulated, the average change varies from a 6% increase to a 23% decrease.

The four patients of Group I-B have been followed in the study for the longest time. Variations in the levels of serum cholesterol are graphically presented in figure 1. During the initial six weeks of medication, each showed a decrease in the level of serum cholesterol; during the interval while medication was withheld, the serum cholesterol increased and, in the case of the female patients, the levels exceeded the average of the original control samples. When medication was again given, a similar drop in the level of serum cholesterol was noted. The two male patients, although exhibiting a large bi-weekly variation, maintained a level of serum cholesterol lower than the premedication values. The female patients did not demonstrate a lasting decrease in the level of serum cholesterol over the interval of the study.

TABLE 2  
Changes in Total Cholesterol: Group II

Subject	Mean of 4 Initial Total Cholesterols (mg./100 ml. serum)	Average % Change From Initial Mean		Lowest Level during Treatment (mg./100 ml. serum)	
		125 mg./daily	250 mg./daily	125 mg./daily	250 mg./daily
D. N.	223	-14	-17	174	178
M. S.	197	-9	1	154	160
M. L.	197	-6	2	163	177
D. K.	207	-10	-15	161	159
G. H.	224	5	6	217	220
S. H.	205	-17	-17	142	139
R. Y.	235	9	18	223	214
T. R.	199	-23	-24	136	107
R. D.	180	-9	-2	141	161
L. C.	201	-10	-7	173	139

Triparanol dosage: 125 mg. daily for 21 weeks, then 250 mg. daily for 17 weeks.

In Group II, it was considered of interest to investigate in one group of patients the effects of two dosages of medication. Ten patients have been followed for 38 weeks. The dosage was 125 mg. daily until the end of the twenty-first week, at which time it was doubled (to 250 mg. daily). The results of this part of the study are presented in table 2. Eight of 10 patients showed an average decrease in the level of serum cholesterol of 6% to 23% at a dosage of 125 mg. daily. When the dosage was increased to 250 mg. daily, only three of the 10 exhibited a further decrease, and this was minimal. Six other patients on the doubled dose of medication failed to maintain the original lower levels of serum cholesterol which had been established with the 125 mg. daily dose.

Body weights of patients varied only slightly during the study.

## DISCUSSION

The data presented tend to support the conclusion that Triparanol does indeed lower the level of serum cholesterol. This is particularly true during the first four weeks of therapy. If the medication is discontinued, the decrease in the level of serum cholesterol is not maintained. The data also suggest that the earlier low levels of serum cholesterol are not maintained during an interval of continuous administration of medication.

It should be emphasized that biologic variation in levels of serum cholesterol may account for the results obtained here. Watkin et al.<sup>6</sup> have reported that, in a study of a large, unselected group of patients, the biologic standard deviation of serum total cholesterol was  $\pm 13.96$  mg. per 100 ml.

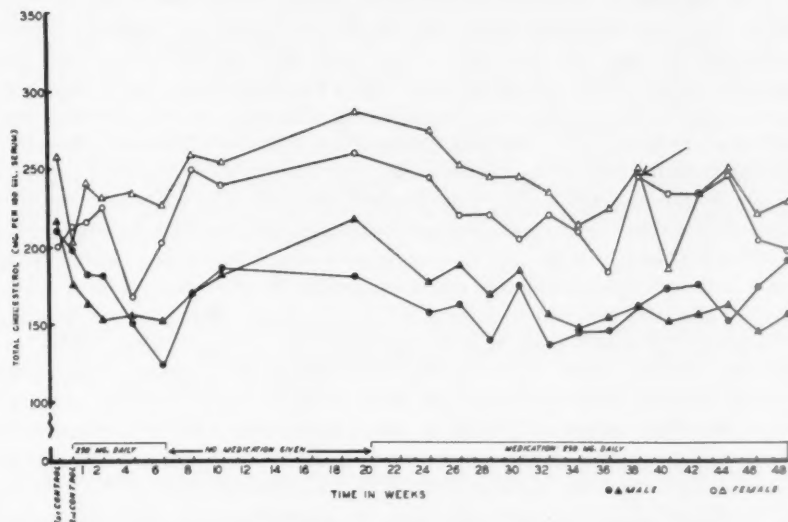


FIG. 1. Effects of Triparanol on level of serum cholesterol, Group I-A. (Arrow indicates level after medication was accidentally omitted for seven days.)

Rivin et al.<sup>5</sup> have observed a biologic deviation of a somewhat higher magnitude in patients with cardiac infarction, and suggest that, to attribute to some medication a therapeutic effectiveness, there should be a decrease in cholesterol of 100 mg.% if only one sample is taken, or of at least 60 mg.% if repeated samples show a sustained lowering.

The variation in response noted at the two dosage levels is in accord with the findings of Oaks et al.<sup>3,4</sup> who, in evaluating Triparanol for a six-week period, observed that the decrease in level of serum cholesterol was not dependent upon the dosage, since the change or decrease in level of cholesterol was larger in their 250 mg. group than in their 500 mg. group, and since

doubling the dosage to 1,000 mg. daily did not produce an effect that might be anticipated by such an increase. In our study, similar results were obtained with 125 mg. and 250 mg. daily dosages. Comparison of these data with those of the previously mentioned authors would suggest that 125 to 250 mg. daily might be the most effective dose.

In view of the limited number of patients, differences in the long-term effects in male and female patients cannot be assessed.

Any inferences drawn from this study must include recognition that the diet was not controlled, that the experimental group did not have an abnormally high level of cholesterol at the beginning of the study, and that, so far as is known, no patients had a preëxisting physical illness, such as coronary heart disease, familial hypercholesterolemia or diabetes mellitus.

The following symptoms occurred in patients who participated in the study, and may represent either side-effects or coincidental findings. Two patients in Group I-A developed a mild rash and were dropped from the study after two weeks of medication. At a later time, the preparation was again given to these patients for eight weeks; the rash returned but was not serious. In Group I-B, one patient developed a low white blood cell count, and medication was discontinued during the twenty-seventh week; medication was administered again at the beginning of the thirtieth week, but was again discontinued during the thirty-fourth week because of a lowered white blood cell count. In Group II, one patient developed a low white blood cell count, and medication was discontinued during the twenty-fourth week. One of the four patients of Group I-A who completed the six-week study was placed 15 weeks later in a group receiving 250 mg. daily. After receiving 250 mg. daily for one week, he developed a chronic congestive cardiac decompensation, and medication was discontinued. When, 12 weeks later, he was again given 250 mg. daily for seven weeks, he had a recurrence of chronic congestive cardiac failure, and medication was again discontinued. A second patient, who likewise completed the six-week study and 15 weeks without medication, was also placed in the group receiving 250 mg. a day, and received medication at that level for 10 weeks, at which time medication was discontinued because of "edema." Six weeks later, medication was resumed for nine weeks, and again was discontinued because of "edema" and influenza. Three weeks later the patient died. (In these two cases, each patient's physician and a consulting internist felt the illnesses were coincidental and were not due to or associated with the medication.)

#### SUMMARY

Triparanol, demonstrated in animals to be an inhibitor of cholesterol synthesis, was evaluated in groups of patients living in two state hospitals for its effect on the level of serum cholesterol. Results of the study, extending over many months, indicate that the medication in many cases



lowers the level of serum cholesterol. The effect is not maintained when the medication is discontinued. Continued administration of the preparation fails to maintain the initial depression in level of serum cholesterol.

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#### SUMMARY IN INTERLINGUA

Triparanol, un inhibitor del synthese de cholesterol, esseva evalutate in patientes in duo hospitales psychiatric public. In un gruppo de sex patientes, recipiente 750 mg per die durante sex septimanas, le cholesterol del sero declinava notabilemente durante le prime septimana, sed le reduceite nivello non se manteneva. In duo patientes masculine, recipiente 250 mg per die durante sex septimanas e, post un intervallo de 15 septimanas sin ulle medication, de novo 250 mg per die durante 27 septimanas, le cholesterol del sero monstrava un reduction initial, sequite per primo un augmento e alora de novo un micre reduction. In duo patientes feminin, con le mesme programma de tractamento, le reduceite nivellos de cholesterol non se manteneva. Un gruppo de 10 patientes recipiente 125 mg per die durante 21 septimanas e alora 250 mg per die durante 27 septimanas non monstrava un sustenite reduction del nivello de cholesterol seral. In iste studio, le dieta non esseva regulate. Le membros del gruppo experimental habeva nulle morbo a parte lor disordines psychiatric e non se distingueva per anormalmente alte nivellos initial de lor cholesterol seral.

#### BIBLIOGRAPHY

1. Avigan, J., Steinberg, D., Thompson, M. J., and Mosettig, E.: Mechanism of action of MER-29, an inhibitor of cholesterol biosynthesis, *Biochem. and Biophys. Research Communications* 2: 63, 1960.
2. Blohm, T. R., Kariya, T., and Laughlin, M. W.: Effects of MER-29, a cholesterol synthesis inhibitor, on mammalian tissue lipides, *Arch. Biochem. and Biophys.* 85: 250, 1959.
3. Oaks, W., and Lisan, P.: A new cholesterol synthesis inhibitor, *Federation Proc.* 18: 428, 1959.
4. Oaks, W., Lisan, P., and Moyer, J.: Inhibition of cholesterol synthesis with the use of MER-29, *Arch. Int. Med.* 104: 527, 1959.
5. Rivin, A. U., Yoshino, J., Shickman, M., and Schjeide, O. A.: Serum cholesterol measurement-hazards in clinical interpretation, *J. A. M. A.* 166: 2108, 1958.
6. Watkin, D. M., Lawry, E. Y., Mann, G. V., and Halperin, M.: Study of serum beta lipoprotein and total cholesterol variability and its relation to age and serum level in adult human subjects, *J. Clin. Investigation* 33: 874, 1954.
7. Zak, B., Dickerman, R. C., White, E. G., Burnett, H., and Cherney, P. J.: Rapid estimation of free and total cholesterol, *Am. J. Clin. Path.* 24: 1307, 1954.

## THE CHEMOTHERAPY OF UREASE- AND CITRASE-PRODUCING BACTERIA OF THE URINARY TRACT \*

By HARRY SENECA, M.D., F.A.C.P., JOHN K. LATTIMER, M.D., F.A.C.S.,  
and HANS H. ZINSSER, M.D., *New York, N. Y.*

### INTRODUCTION

BEGINNING with the premise that magnesium ammonium phosphate stones formed in the urinary tract were primarily the result of the enzymatic urea-splitting capacities of some types of urinary tract pathogens, both Gram-positive and Gram-negative, the possibilities of blocking this enzyme were explored by Walberg from 1951 to 1956.<sup>1</sup> The kinetics and characteristics of some of the bacterial urea-splitting enzymes were elucidated, and several potent inhibitors were described.<sup>1</sup> Shortly after this approach was applied clinically, it was found that the capacity of chlormerodrin to change the urinary pH to the acid side resulted in considerable dissolution of struvite stones within the urinary tract, and that, after discontinuance of administration of the drug, the urinary pH remained persistently acid in many cases.<sup>2</sup> This was at first thought to be due to adsorption of the organic material to stones still in place, but as it had already been shown that the drug was not effectively adsorbed to the surface of the bacterial cells in question,<sup>1</sup> more detailed study of the organisms themselves after exposure to orally administered chlormerodrin to the host was carried out.

Surprisingly many of the strains were no longer capable of splitting urea and, in addition, many of them previously resistant to a variety of antibiotics were now susceptible to them. We have already obliquely referred to this finding in previous presentations.<sup>3, 4, 5</sup> The correlation of enzymatic capacities and antibiotic sensitivity and resistance has been worked out in detail in only a few instances, but they seem to have general validity.<sup>6</sup>

The capacities of heavy metal ions to inactivate a variety of enzyme systems through their capacity to react with sulfhydryl active sites would not seem to be the only mode of action operating in this instance.<sup>7</sup> There is apparently some evidence for a long-standing change in the nature of the organisms themselves on a kinetic basis. The mutagenic effect of heavy metal ions when applied in sublethal concentrations may in part be related

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From the Department of Urology, Columbia University College of Physicians & Surgeons, New York, N. Y.

Requests for reprints should be addressed to Harry Seneca, M.D., Columbia University (P & S), New York 32, N. Y.

to the firmer binding due to the accessory orbitals available for binding not found in the normally occurring alkaline earth metals in genetic material.<sup>8, 9, 10</sup>

Urine is a complex medium for bacterial growth, capable of supporting life of organisms manifesting complex nutritional requirements. It has become apparent that some of the organisms most difficult to control in clinical urologic infections are those with very simple requirements, utilizing substrates for which metabolic blocking agents are only now being devised. An interesting example involves the use of fluoro-acetate to block the utilization of citrate in the mammalian organism.<sup>11</sup> We have been struck in particular with the fact that organisms capable of surviving with citrate and urea as the sole substrate are peculiarly resistant to most antibacterial agents in common use at the present time.<sup>12</sup>

#### MATERIALS AND METHODS

Strains of pathogenic bacteria, both Gram-positive and Gram-negative, derived from clinical cases of genitourinary infection at the Squier-Urological Clinic, were studied extensively by tube dilution technics for antibiotic susceptibility. In addition, their susceptibilities to enzyme inhibition and survival on a variety of simple substrates, in particular Bacto urea, Simmon's citrate, SAT medium, citrate and urea agar, were analyzed as described previously.<sup>13</sup> In patients with clinical infection the antibiotic sensitivities were initially determined, the patient was given oral doses of mercurial diuretic known by a previous tracer experiment<sup>14</sup> to be excreted in the urine in low concentration, and bacterial sensitivities of the organisms were subsequently determined and their identification repeated, utilizing routine bacteriologic methods.

For the purposes of identification and specific species subtyping, known strains derived from U. S. Army and U. S. Navy medical laboratories and the U. S. Public Health Service were also surveyed. Organisms have been subdivided on their urease and citrase capacities into seven groups which correspond roughly to their susceptibility to antibacterial agents (table 1).

#### RESULTS

Our success with the use of enzyme-blocking agents to acidify the urine in cases of intractable urea-splitting infection has been previously described.<sup>2</sup> In the group of 37 patients with retained struvite stones secondary to urea-splitting infection, the urinary pH was invariably reversed; but after a time for minimal dissolution to take place, these stones became obstructive and surgery was required to achieve a cure. Judicious use of acidifying agents, with or without enzyme-blocking agents, has been uniformly successful in avoiding recurrence over a limited period of time. This will be reported in greater detail at a later date.

TABLE 1  
Enzyme Profile, Biochemical Reactions and Resistance Pattern of Pathogenic Bacteria

Profile	Enzyme		Enzyme Media					Resistance Pattern						Carbohydrates						
	Urease	Citrate	Bacto Urea	Simmon's Citrate	Urea Citrate	Urea	Citrate	Nitrofurantoin	Sulfisoxazole	Tetracycline	Chloramphenicol	Erythromycin	Penicillin Streptomycin†	Colymycin	Lactose	Dextrose	Maltose	Mannitol	Saccharose	
Profile 1 <i>Proteus columbiensis</i> <i>P. vulgaris</i> <i>P. rettgeri</i> <i>P. mirabilis</i> <i>P. OX 2</i>	+	+	S/B	S	S/B	S	+	R	R	R	R	R	R	S	—	AG	AG	—	AG	
	+	+	S/B	S	S/B	S	+	R	R	R	R	R	R	S	—	A/AG	—	A/AG	—	
	+	+	S/B	S	S/B	S	+	R	R	R	R	R	R	S	—	AG	—	—	—	
	+	+	S/B	S	S/B	S	+	R	R	R	R	R	R	S	—	AG	—	—	—	
	+	+	S/B	S	S/B	S	+	R	R	R	R	R	R	S	—	AG	—	—	—	
Profile 2 <i>P. mirgani</i> 69% of <i>Micrococcus</i> <i>Proteus vulgaris aerogenes</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> 77% of <i>Pseudomonas aeruginosa</i>	+	—	S/B	—	S/B	—	—	R	S	R/S	R/S	R/S	R/S	—	A	A	A	A	—	
	+	+	S	S	S	—	—	R	R	R	R	R	R	—	AG	AG	AG	AG	AG	
	+	+	S	S	S	—	—	R	R	R	R	R	R	—	AG	AG	AG	AG	AG	
	+	+	S	S	S	—	—	R	R	R	R	R	R	—	AG	AG	AG	AG	AG	
	+	+	S	S	S	—	—	R	R	R	R	R	R	—	AG	AG	AG	AG	AG	
Profile 3 <i>P. OX 19</i> <i>P. OX K</i> <i>P. inconstans</i>	—/+	—/+	—/S	—/S	—/S	—/S	—	R	S	S/R	S	S/R	S	—	—	A/AG	—	—	—	
	—	—/+	—	S	S	S	+	R	S	S	S/R	R	R	—	—	—	—	—	—	
	—	—/+	—	S	S	S	+	R	S	S	S/R	R	R	—	—	—	—	—	—	
	—	—/+	—	S	S	S	+	R	S	S	S/R	R	R	—	—	—	—	—	—	
	—	—/+	—	S	S	S	+	R	S	S	S/R	R	R	—	—	—	—	—	—	
Profile 6 23% of <i>Pseudomonas aeruginosa</i> <i>Alcaligenes faecalis</i> <i>Salmonella</i> <i>Vibrio cholerae</i> <i>Escherichia (freundii, intermedia)</i> <i>Escherichia (coli, avrescens)</i> <i>Escherichia typhosa</i> <i>Salmonella (paratyphi, pullorum, gallinarum)</i> <i>Vibrio El Tor</i> 31% of <i>Micrococcus</i> <i>Enterococcus</i> <i>Streptococcus pyogenes</i> <i>Shigella</i> <i>Pneumococcus</i>	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	AG	AG	AG	—	
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—
	—	—	+	—	—	—	—	R	S	S	S	S	R	—	—	—	AG	AG	AG	—

+ = growth. — = no growth reaction. A is acid. AG = acid and gas. S = slant. B = butt in media. S = sensitive. R = resistant.

In a second group of 64 patients infected with drug resistant pathogens, 43 cases were thoroughly studied, with cultures taken before and after chlormerodrin therapy. These patients were given one tablet of chlormerodrin, four times daily, for four days. This was followed by the administration of the chemotherapeutic of choice, selected on the basis of sensitivity by the tube dilution method.

Eighteen patients were cured of their infection with chlormerodrin alone. They had 19 pathogens, namely, *E. coli* in three patients, *A. aerogenes* in two, *P. aeruginosa* in three, *B. proteus* in one, *M. pyogenes aureus* in eight and enterococcus in two patients. Seven other patients who were cured were reinfected with eight pathogens, namely, *A. aerogenes* in two cases, *P. aeruginosa* in one, *B. proteus* in four and enterococcus in one patient. Eighteen other patients failed to respond to chlormerodrin therapy. They had 21 pathogens, i.e., *E. coli* in three patients, *E. intermedia* in one, *A. aerogenes* in six, *P. aeruginosa* in four, *B. proteus* in two, *P. morgani* in one, *M. pyogenes aureus* in one and enterococcus in three patients.

Drug sensitivity pattern among the pathogens which failed to respond to chlormerodrin therapy showed no changes in seven pathogens, i.e., one *E. intermedia*, three *A. aerogenes*, one *B. proteus* and two enterococci. Four pathogens showed increased sensitivity to drugs: two *E. coli* became more sensitive to sulfadiazine, tetracycline, demethylchlortetracycline, chloramphenicol and nitrofurantoin; one *A. aerogenes* became more sensitive to sulfadiazine, and one *M. pyogenes aureus* became more sensitive to Colymycin. Three pathogens became more resistant to drugs: one *E. coli* became more resistant to sulfadiazine, tetracycline, and demethylchlortetracycline; one *A. aerogenes* became more resistant to sulfadiazine, and one enterococcus became more resistant to tetracycline, demethylchlortetracycline and chloramphenicol, but there was no change in the sensitivity pattern to the other drugs tested.

Both the morphology and the cultural characteristics of the bacteria under attack with the enzyme-blocking agent have been severely changed. As it is well known that superinfection in such patients is a common occurrence, in general with organisms from the gastrointestinal tract, as we have previously shown, we have been guarded in our claims that real mutagenic change has been produced in the bacteria in the host. As all of these organisms undergo spontaneous mutation in response to increasing levels of antibiotics in the medium, and as they may readily incorporate deoxyribose nucleic acid (DNA) from the dying members of parallel strains,<sup>15</sup> only rigorous in vitro work can establish that real genetic transformation has taken place. The bacteriology in vivo of these patients shows drastic changes, which are simulated in part by the changes demonstrated by in vitro exposure of the bacteria to sublethal quantities of the mercurial agent utilized.

A serious drawback to long-range conclusions at a theoretic level is the

fact that the bacteria have in some instances become bizarre with respect to bacteriologic studies. Unlike the changes induced by the effect of penicillin on the cell walls, the morphologic changes and biochemical changes are suggestive of new bacteriologic species.

Starting as we have done almost invariably with highly resistant strains, we find that the changes induced by this therapy have by no means been for the good as regards antibiotic susceptibility. It should be emphasized that changes in a deleterious direction may well be possible, and the application of these agents should therefore be somewhat guarded. Indeed, in many instances *in vitro* we have been able by such manipulation to derive strains that were more resistant rather than less resistant. More detailed study of the enzymatic capabilities of these organisms is under way.

#### DISCUSSION

In genitourinary infections in the hospital the bacterial population is continuously reinforced by adventitious organisms from the outside. This can produce a changing population, in which the most resistant organisms survive for the longest period of time. Each new antibiotic is used in the treatment of the more desperate cases and with the survival of such patients, further seeding of the environment with a new and hardier bacterial breed takes place.

We have been plagued in the last few years by a rather resistant *Aerobacter aerogenes* which was at first Kanamycin-sensitive, and which seemed peculiarly resistant to other conventional agents. An increasing proportion of our hospital population is subjected to *Pseudomonas* infection, in the treatment of which Colymycin seems to be of particular usefulness. The urease inhibitors are not promising here, or in urease-citrate-negative pathogens, as might have been suspected. *Proteus* infections have been unusually labile under the impact of enzyme-blocking agents, and it is with them and with the staphylococci that we have had most success clinically with this approach.

It is apparent that, if we are to cope successfully with succeeding waves of invaders, a capacity to induce useful changes in the bacteria must be implemented by a wider armamentarium. We believe that, with substituted organic materials as widespread enzyme-blocking agents, we may be able to affect favorably the course of many clinical infections.

Among the possible sites of action which we have described, certainly the modification of disulfide linkages in the enzymes themselves is an attractive possibility. The long-acting effect would seem, however, to speak more for the incorporation of mercury into abnormal cross-links in the phosphate residues of the genetic material of the bacteria themselves. That this may well affect the functioning of ribonuclease itself seems entirely possible, although we have no experimental evidence as yet.



## SUMMARY

1. The addition of a period of exposure to chlormerodrin in doses of 36.6 to 55.8 mg. per day has reversed the alkalinity of the urine in patients harboring urease-positive bacteria.

2. The persistence of this pH-reversing effect can be shown to imply a profound change in the metabolism of the bacteria themselves.

3. Subsequent to this change in enzymatic capacities of the bacterium, which is apparently transmitted genetically from generation to generation within the given strain, their sensitivity to a variety of antibacterial agents has changed, in some instances favorably, but by no means so in every instance.

4. As the most resistant organisms found in the urinary tract exhibit both urea- and citrate-utilizing capacity, the addition of organic mercurials to a therapeutic regimen, particularly in the presence of stone, seems justified at this time.

## ACKNOWLEDGMENT

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## SUMMARIO IN INTERLINGUA

Super le base del production de urease e de citrase per bacterios pathogene, septe profilos pote esser distinguite. Productores de urease e de citrase (*B. proteus*, *Aerobacter*, *Klebsiella*, e *Pseudomonas*) es altemente mutagenic e chimo-resistente, o illos acquire prestemente un resistentia a chimicales. Bacterios que es productores de solmente urease (*Proteus morganii*, micrococcus, e enterococcus) o de solmente citrase (*Alcaligenes*, *Salmonella*, *Vibrio*) es minus mutagenic e minus resistente a drogas. Del altere latere, bacterios que produce nulle enzima del toto (*Escherichia*, *Eberthella*, *Shigella*, *Streptococcus pyogenes*, enterococcus) es sensibile al drogas.

In vitro, agentes que bloca urease—per exemplo mercuriales organic (chlormerodrina)—modifica le physiologia e le morphologia del bacterios, rendente los assi plus sensibile al effecto de drogas, ben que in certe casos il etiam occurre que mutantes resistente es producite.

Quatro tabletas de chlormerodrina reverteva le alcalinitate del urina in pacientes albergante bacterios de typos ureasogene. Il es possibile monstrar que iste effecto de un reversion del pH resulta in un profunde alteration del metabolismo del bacterios, con le consequente modification de lor sensibilitate pro varie agentes antibacterial. Iste modification es frequentemente favorabile, sed non in omne le casos. Il es possibile que le sito del action es le ligamine disulfidic in le enzymas mesme. Il es etiam possibile que ille action consiste in le incorporation de mercurio in anormal nexos transverse in le residuos de phosphato del material genetic del bacterios, con le effecto de un alteration functional de ribonuclease mesme.

## BIBLIOGRAPHY

1. Walberg, C. B.: The purification and properties of bacterial urease, thesis, University of Southern California School of Medicine, 1957.
2. Zinsser, H. H., Lattimer, J. K., and Seneca, H.: Aerogenesis: a plea for clinical bacteriology, to be published.

3. Lattimer, J. K., Seneca, H., Zinsser, H. H., and Troc, O. K.: Increasing seriousness of resistant urinary infections with *Aerobacter aerogenes*, J. A. M. A. **170**: 938, 1959.
4. Seneca, H.: *Aerobacter aerogenes* bacteremia and bacilluria, Surg., Gynec. and Obst. **108**: 733, 1959.
5. Seneca, H., and Troc, O. K.: Implications of maximal bacterial resistance to antibiotics, Postgrad. Med. **26**: 457 (Oct.) 1959.
6. Seneca, H., Zinsser, H. H., and Lattimer, J. K.: Relation of drug resistance to enzyme activity among coliform bacteria, J. A. M. A. **172**: 1015, 1960.
7. Hellerman, L.: Reversible inactivation of certain hydrolytic enzymes, Physiol. Rev. **17**: 454, 1937.
8. Wacker, W. E. C., and Vallee, B. L.: Nucleic acids and metals, J. Biol. Chem. **234**: 3257, 1959.
9. Wacker, W. E. C., Fuwa, K., and Druyan, R.: Structural determinants of RNA, Federation Proc. **19**: 319 (Mar.) 1960.
10. Felsenfeld, G., and Huang, S.: The interaction of polynucleotides with metal ions, amino acids and polyamines, Biochim. et Biophys. Acta **37**: 425 (Jan. 29) 1960.
11. Johnson, R. G.: Prevention and dissolution of calculi in rats with fluoroacetate and citric acid, J. Urol. **82**: 261 (Aug.) 1959.
12. Seneca, H., Milner, P., and Troc, O. K.: Clinical laboratory classification of proteus on the basis of its biochemical potentialities, Read before the Association for the Advancement of Science, Dec., 1959.
13. Seneca, H., Milner, P., and Troc, O. K.: Enzyme profile of *B. proteus*, to be published.
14. White, S., and Nuhfer, P. A.: The diuretic activity and urinary excretion of three new mercurial compounds when administered intravenously, J. Pharmacol. and Exper. Therap. **101**: 38, 1951.
15. Catlin, B. W.: Interspecific transformation of neisseria by culture slime containing deoxyribonucleate, Science **131**: 608 (Feb.) 1960.

## FATAL MYXEDEMA, WITH AND WITHOUT COMA \* †

By JOHN F. NICKERSON, ‡ S. RICHARDSON HILL, JR., M.D., JEAN H. MCNEIL, M.D., § and SAMUEL B. BARKER, Ph.D.,  
*Birmingham, Alabama*

### INTRODUCTION

RELATIVELY few cases of terminal myxedema, especially of myxedema coma, have been reported. The first report of fatal hypothermic coma appeared in 1879.<sup>1</sup> The condition was also described in 1888, in the report on myxedema of the Clinical Society of London.<sup>2</sup> However, it was not brought to general attention until 1953, when six cases were reported in two series.<sup>3,4</sup> Twenty-four additional case reports have appeared in the last six years.<sup>5-21</sup> It is noteworthy that 13 of the 30 case reports have been in four series.

In contrast to the scarcity of reported cases of terminal myxedema, during the last three years we have observed four patients with severe myxedema who died without responding to replacement therapy, and one in semicomma who recovered with therapy. Because of this relative frequency and high mortality, a reevaluation of the problem and of the present unsatisfactory therapeutic regimen was deemed warranted.

### MATERIALS AND METHODS

All five patients in the present study were females (ranging in age from 48 to 71) in whom a clinical and laboratory diagnosis of severe hypothyroidism had been established. The serum protein-bound iodine determinations were done by a modification of the method of Barker.<sup>22</sup> The normal range for this laboratory is 4.0 to 8.0  $\mu\text{g.}\%$ . The percentage of radioactive iodine uptake over the thyroid was determined at 24 hours with the conventional scintillation probe counter. The normal range in this laboratory is 10 to 45%. The basal metabolic rate was determined by the Benedict-Roth technic. The lowest value obtained in a series of determinations was accepted as being most reliable.

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From the Division of Metabolism and Endocrinology, the Departments of Medicine and Pharmacology and the University Hospital, University of Alabama Medical Center, and the Medical Service, Veterans Administration Hospital, Birmingham, Alabama.

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‡ Student Fellow, National Institutes of Health, Bethesda, Maryland.

§ Trainee, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland.

Requests for reprints should be addressed to S. Richardson Hill, Jr., M.D., Associate Professor of Medicine, The University of Alabama Medical Center, Medical College of Alabama, Birmingham 3, Alabama.

Parenteral triiodothyronine is not commercially available. That used in this study was prepared as needed by dissolving triiodothyronine sodium in 0.1 normal NaOH. Distilled water and 10% NaCl solution were added, so that the final concentrations were 0.85% NaCl, 0.05 normal NaOH, and 30  $\mu$ g. of triiodothyronine per milliliter. The final concentration of triiodothyronine is the absolute concentration and not that of the sodium salt. This preparation can be used either intravenously or intramuscularly.

#### CASE REPORTS

*Case 1.* A 71 year old white female was admitted to the private surgical service on April 10, 1956, with abdominal pain and distention. The patient had first been seen in the medical clinics in 1947 for nonexertional chest pain radiating to the left arm, nervousness and crying spells. Dermatitis of both lower extremities was noted at that time, and she was followed by the dermatology clinic for six months. In 1948 it was noted that she appeared to be both myxedematous and jaundiced. A serum cholesterol level was reported as 157 mg.%, and a serum icterus index was 5 units. The patient received no further evaluation or treatment at that time. She was subsequently referred from one clinic to another, with frequent notations made of the psychoneurotic overlay in the case. One observer in 1951 noted that her history was compatible with myxedema, and started her on 15 mg. of desiccated thyroid daily. She returned to the clinic only once after that visit, and still had many of the same complaints. She stopped taking her desiccated thyroid shortly thereafter. The patient was seen again in June, 1953, and was hospitalized by a private physician for the complaints of abdominal swelling and severe constipation of three months' duration. She had marked abdominal distention with a fluid wave and shifting dullness. She was treated with enemas and Prostigmin after a radiologic diagnosis of megacolon was made.

The patient was not seen again until April 10, 1956, at which time she was admitted to the private surgical service with severe abdominal pain and distention, which had been becoming progressively more severe since her previous admission. Her temperature was 99° F.; pulse, 76; blood pressure, 122/86 mm. Hg. The tongue, skin and mucous membranes were dry. The lung fields were clear. There was a normal sinus rhythm, with no cardiac murmurs or enlargement. No abdominal organs or masses were palpable, but there was marked distention. On auscultation of the abdomen only an occasional high-pitched, tinkling sound was heard. Cecostomy was performed on April 11 for relief of the distention. The patient was reported as much improved following operation, but the next day she was lethargic and responded poorly. Her blood pressure was 86/64 mm. Hg, but it rose slightly following a blood transfusion. Her temperature varied from 99° F. to 101° F. Her condition gradually deteriorated, and on April 19 myxedema was suggested as a cause of the increasing stupor. A protein-bound iodine drawn at that time was 1.0  $\mu$ g.%. Because of progressive unresponsiveness, a tracheostomy was necessary on April 21. The patient was treated with multiple antibiotics, calcium gluconate, potassium chloride, blood, pooled plasma and electrolyte solutions, with no clinical response. On April 25 she received 10  $\mu$ g. of triiodothyronine and 100 mg. of hydrocortisone dissolved in 1,000 c.c. of 5% dextrose in water intravenously. Cortisone was continued intramuscularly, in doses of 25 mg. every 12 hours. The following morning the blood pressure was 40/30 mm. Hg, and administration was begun of an intravenous infusion of norepinephrine, along with 30  $\mu$ g. of triiodothyronine and 100 mg. of hydrocortisone dissolved in 1,000 c.c. of 5% dextrose and water. The patient showed no response, and died at 1:00 p.m. on April 26, 1956.

Urinalysis revealed 1 to 3 red cells and 30 to 60 white cells per high power field, and no glucose or protein. Blood urea nitrogen levels ranged from 7.0 to 12.0 mg.%; serum sodium levels, from 129 to 132 mEq./L.; potassium, from 3.8 to 4.0 mEq./L.; chloride, from 84 to 95 mEq./L.; CO<sub>2</sub>, from 15.3 to 25.3 mEq./L.; calcium, from 6.3 to 8.6 mg.%; and cholesterol, from 84 to 91 mg.%. The hematocrit was 38% before transfusion and 44% after transfusion. The plasma prothrombin time was 100%. The fasting blood sugar level was 72 mg.%. The serum level of total protein was 4.4 gm.%, with albumin, 2.3, and globulin, 2.1 gm.%. The serum cephalin flocculation was 2 plus in 24 hours and 3 plus in 48 hours. The serum thymol turbidity was 0 units. The patient had 13% bromsulfalein retention at 45 minutes. The serum protein-bound iodine level was 1.0 µg.% before treatment and 1.4 µg.% on the day of death. The electrocardiogram showed ST segment changes and first degree heart block.

At autopsy the patient was noted to be an obese white female weighing 54 kg. Her general appearance was typical of myxedema. The abdominal cavity contained 250 c.c. and each pleural cavity contained 150 c.c. of straw-colored fluid. Both lungs were small, and cut sections showed atelectasis and minimal congestion. The pericardial cavity contained no fluid, and the heart weighed 410 gm. No valvular lesions were present. The coronary arteries were patent, with only minimal atherosclerosis. The aorta was moderately atherosclerotic. The pulmonary arteries were patent, with only a slight degree of atherosclerotic streaking. The weight of both adrenals was 19 gm. Two small ulcers were present along the lesser curvature of the stomach. The liver weighed 1,430 gm., and a yellowish mottling and mild congestion were present on cut section. The gall-bladder, pancreas and spleen appeared to be normal. There was marked dilatation of the ascending, transverse and descending colon. At the approximate level of the rectosigmoid there was a constriction of the bowel. On cut section this appeared to be inflammatory rather than neoplastic. The left kidney weighed 180 gm., the right, 170 gm., and the surface of both was finely granular. The pelvic organs were not remarkable. The brain weighed 1,200 gm., and no gross abnormalities were noted. The pituitary was normal in appearance. The thyroid weighed 7.5 gm. Multiple microscopic sections of the thyroid revealed that most of the parenchyma had been replaced by loose, fibrofatty tissue. Scattered microscopic areas contained a few follicles of varying size composed of oxyphil cells. Marked lymphocytic infiltration was present throughout the remains of the gland, but was most marked at the periphery of these follicles. Sections of the heart revealed calcification of the mitral ring. The lungs were mildly emphysematous and congested. The adrenals were normal histologically. The liver showed a mild degree of centrilobular atrophy and periportal lymphocytic infiltration. Sections of the stomach ulcers showed no neoplastic cells. Sections of the colon revealed melanosis coli, numerous chronic ulcers, and rather marked hypertrophy of the muscularis. The area of colonic constriction was composed of fibrous tissue. Sections of both kidneys showed periglomerular fibrosis. The remaining microscopic sections, including those of the pituitary and the parathyroid glands, were normal. The thyroid changes were thought to be a fibrous variant of struma lymphomatosa.

*Comment:* Although the patient had presented the typical clinical picture of myxedema for eight years before her final admission and death in 1956, replacement therapy with thyroid was given for only a brief period in 1951. It is obvious that the intravenous triiodothyronine had little effect on the patient's clinical course. A major factor in this ineffectiveness was undoubtedly the delay in its administration, and the amount given may have been too small. The low serum cholesterol level aroused clinical suspicion

as to secondary hypothyroidism. The autopsy findings, however, were those of primary thyroid atrophy associated with grossly and microscopically normal pituitary and adrenal glands. The case was atypical in that hypothermia was not a feature. Hypometabolic coma was thought to be the cause of death, as no other disease entity of life-endangering import was demonstrated clinically or at autopsy.

*Case 2.* A 48 year old white female was admitted on July 3, 1958, with vaginal bleeding of two months' duration. Although she gave a history of frequent menorrhagia, the source of bleeding on this occasion was a laceration of the external genitalia. The remaining gynecologic evaluation was negative. In addition, she had paraplegia and marked generalized weakness which had begun in childhood. As a child she had been obese and mentally retarded. Private schooling was begun at age 10, but this was soon terminated by a progressive muscular weakness, atrophy and lack of coordination. Six years before admission the patient had fallen and fractured her right ankle. Since that time she had been confined to bed. In April, 1957, she had had a left nephrectomy for a stag-horn calculus, and in July, 1957, she

#### Relationship of the Patient's Temperature to the Environmental Temperature.

C.B., 48, F. Dx.: Myxedema

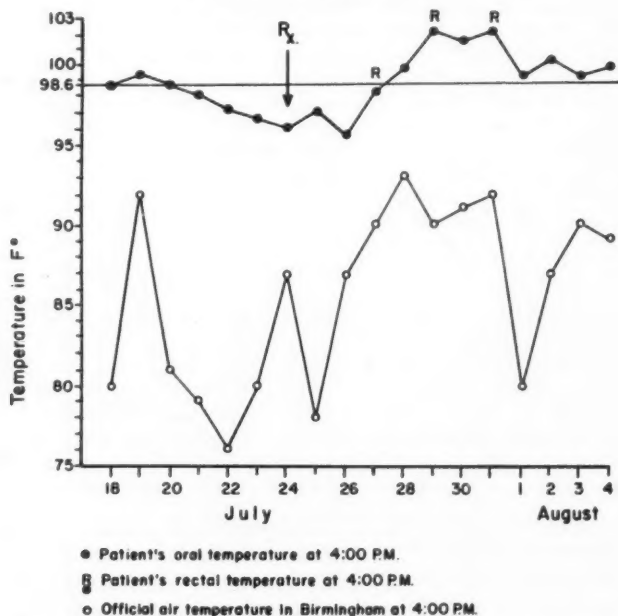


FIG. 1. A graphic representation of the relationship of the body temperature of case 2 and the air temperature at 4:00 p.m. This patient became hypothermic during a period of relatively low temperatures for July in this area. Three of the readings were recorded rectally (R).



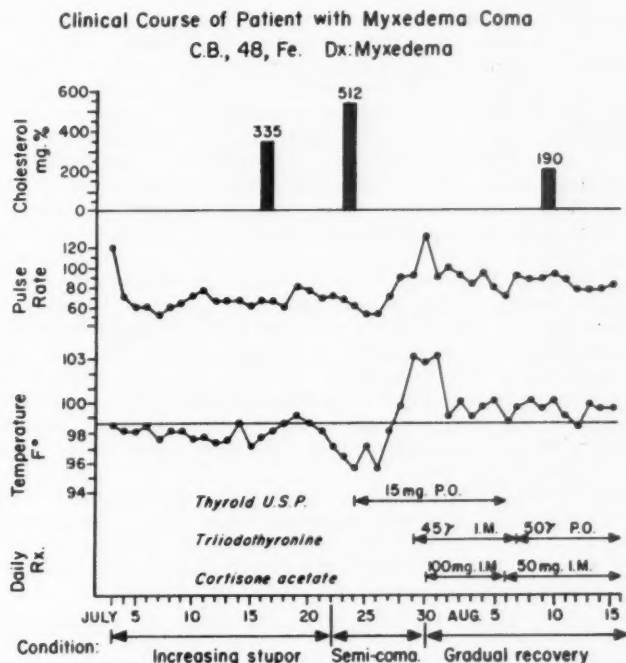


FIG. 2. The clinical course of case 2, who developed myxedema stupor and hypothermia during the summer months. She showed gradual but marked improvement on oral desiccated thyroid and parenteral triiodothyronine.

had a right nephrostomy for a stag-horn calculus. For the three months prior to admission she had been becoming progressively more stuporous and hoarse.

The patient was poorly developed, relatively well nourished, and extremely lethargic. The blood pressure was 130/85 mm. Hg; respiration, 22; pulse, 86; temperature, 98.6° F. Her head hair was thinly distributed and coarse. The pupils were miotic, with only a sluggish reaction to light. The tongue was enlarged. The thyroid was not palpable. The thorax was symmetric. The respiratory movements were reduced and the breath sounds were distant. Examination of the heart was remarkable only in that the heart sounds were distant. The abdomen was soft, with no masses or tenderness. The fingers were tapered and hyperextended, and the patient had difficulty relaxing her grip. The legs were atrophic and flaccid, with a bilateral foot drop and pitting pedal edema. The deep tendon reflexes were absent in the lower extremities and reduced in the upper extremities. The only sensory defect noted was a decreased vibratory sense in the lower extremities. The Babinski reflex was not present.

Urinalysis showed numerous white blood cells per high power field, and 4 plus protein. The packed cell volume was 32%, and the white count was 7,100 per cubic millimeter, with a normal differential. The following values were reported: blood urea nitrogen, 13 mg.%; serum sodium level, 144 mEq./L.; serum potassium level, 2.5 mEq./L.; serum CO<sub>2</sub> level, 30 mEq./L.

A diagnosis of myxedema was considered, and was confirmed by a 24-hour radioiodine uptake of 4% and a serum cholesterol level of 512 mg.%. The serum protein-bound iodine level was 4.9  $\mu$ g.%. The basal metabolic rate could not be satisfactorily obtained. The patient became progressively more lethargic and oliguric, and developed hypothermia despite the high environmental temperature (figure 1). The low-normal serum protein-bound iodine level was not consistent with the clinical picture or the other laboratory findings. The patient was considered to be in impending myxedema coma, and desiccated thyroid, 15 mg. daily, was started on July 24, 1958 (figure 2). Her reduced urinary output was thought to be due to dehydration, and she was placed on tube feeding. At that time her serum sodium level had dropped to 116 mEq./L., but the serum potassium level had returned to a normal value of 4.0 mEq./L. On July 26 she was noted to be very lethargic and unable to sit up in bed. On July 27 her urinary output increased to a normal level, but she was still very lethargic. She was then placed on 15  $\mu$ g. of triiodothyronine intramuscularly every eight hours in addition to her oral thyroid. On July 31 she was markedly improved, and the serum sodium level had risen to 135 mEq./L. Throughout this period the patient requested a sheet to cover herself and complained of being cold, although no shivering was noted. Intramuscular cortisone was also given. The serum cholesterol level dropped from 512 mg.% before thyroid medication to 190 mg.% on August 11, 1958.

A muscle biopsy obtained before treatment demonstrated areas of focal atrophy with vacuolization and fragmentation of many muscle fibers. The patient gradually improved and was discharged August 16, 1958, on 90 mg. of desiccated thyroid daily. She continued to improve as to sensorium and general appearance, and at the end of 12 months is more alert than during any previous period in her life.

*Comment:* Relatively large quantities of thyroid medication, given both orally and parenterally, effected a reversal of the myxedema stupor in this patient. The contribution of the cortisone to this recovery can only be speculative. The duration of hypothyroidism and its possible contribution to her neuromuscular disorder are unknown. Although muscle lesions have been reported in myxedema, none of this severity and duration has been encountered in which a definite etiologic association with the myxedema could be made.

This patient is particularly interesting in that she became definitely hypothermic during the summer months. If this had occurred during a period of low environmental temperature, she undoubtedly would have been much more hypothermic, and perhaps more refractory to treatment.

The low serum sodium concentration seen in this patient is a frequent finding in patients with severe myxedema,<sup>28</sup> and probably contributed to the dull sensorium and weakness.

*Case 3.* A 53 year old Negro female was first seen in the Endocrine Clinic on April 22, 1958, 19 days before her admission and death. Her complaints were those of cold intolerance, anorexia, malaise, exertional dyspnea, somnolence, upper abdominal pain, and constipation progressing in severity over the last year. The patient had been somewhat obese and intolerant of cold all of her adult life. Otherwise, she had considered herself to be in good health. She had a normal menstrual history, and had been pregnant four times, with the last delivery in 1932. A clinical diagnosis of myxedema was substantiated by basal metabolic rates ranging from minus 19 to minus 32%; a 24-hour radioiodine uptake of 7%, and a serum protein-

bound iodine level of 2.1  $\mu\text{g.}\%$ . The serum cholesterol level was 279  $\text{mg.}\%$ . On April 29, 1958, the patient was placed on 15 mg. of desiccated thyroid daily.

The patient was seen again on May 10, 1958, complaining of abdominal pain and swelling. The pain was most intense in the epigastric region, without relationship to meals or position. In addition, she had a low lumbar pain unassociated with urinary tract complaints, and a greatly exacerbated shortness of breath. She had had no bowel movements for the previous four days. She denied chills, fever, nausea or vomiting. She stated that she had taken her thyroid as directed.

The patient was a grossly obese Negro female, with thick, dry, scaly skin and nonpitting edema. She was fairly well oriented but was not alert, and spoke in a coarse, slurred voice. Her blood pressure was 118/76 mm. Hg; pulse, 96; temperature, 100° F.; respiration, from 16 to 30. Her hair was coarse for her race, and her tongue was enlarged. The thyroid was not palpable. The thorax was increased in the anterior-posterior diameter. The diaphragms were elevated, and scattered coarse râles were heard at both lung bases. The respiratory movements were reduced, and a Cheyne-Stokes pattern was present. The point of maximal impulse was diffusely located in the fourth and fifth intercostal spaces outside the midclavicular line. No murmurs were auscultated, and a normal sinus rhythm was present. The abdomen was heavily striated and pendulous, tympanitic throughout, and tender to deep palpation. Only an occasional bowel sound was heard. The deep tendon reflexes were hypoactive and equal. The Babinski reflex was not present. The clinical impression was that the patient had severe myxedema and alveolar hypoventilation, with a possible low grade pancreatitis.

An electrocardiogram demonstrated a right axis deviation. A film of the abdomen revealed intestinal gas in the upper abdomen, but no gas pattern or fluid levels in the lower abdomen. Fourteen hours after admission the patient was turned in bed from her right side to her back and respirations ceased. She was turned back on her right side and respirations started again in a Cheyne-Stokes pattern. Respirations ceased after several more minutes. Shortly before death her pulse was 108; temperature, 98.0° F.; respiration, 42. No change in her clinical picture was noted at that time. The urine on admission contained 1 plus albumin and 5 to 7 white blood cells per high power field. The blood glucose level was 122  $\text{mg.}\%$ ; serum  $\text{CO}_2$  level, 33  $\text{mEq./L.}$ ; serum amylase level, 72 units. The hematocrit was 38% and the white blood cell count, 7,500 per cubic millimeter, with a shift to the left. Autopsy permission was not granted.

*Comment:* It was apparent that this myxedematous patient did not respond clinically to replacement therapy with 15 mg. of desiccated thyroid daily, administered orally over a two-week period. The immediate cause of death can only be speculative. There is little doubt, however, that myxedema played a predominant role in the events leading to her death.

*Case 4.* A 63 year old white female was admitted to the University Hospital on May 14, 1958, with dysphagia, malaise, exertional dyspnea and easy bruising of several weeks' duration. She had been in good health except for chronic constipation of five years' duration. For the previous four weeks, however, she had been able to swallow only liquids. She had had such severe malaise and dyspnea that she had found it difficult even to walk about her home. Pitting pedal edema of recent onset had been noted.

The patient was very lethargic and responded only to questions. She had a pale but yellow-tinged color to her scaly skin. Ecchymotic lesions were noted on the posterior surfaces of both upper and lower extremities. The blood pressure was 110/68 mm. Hg; pulse, 84; respiration, 22. The pupils reacted slowly to light. The

fundi were normal. The patient's tongue was enlarged. A firm, movable, nontender 1 cm. mass was palpated in the left supraclavicular region. The thyroid was not palpable. The antero-posterior diameter of the chest was increased. Inspiratory wheezes were heard in both lung bases and in the left hilar area. The cardiac point of maximal impulse was in the fifth intercostal space at the midclavicular line. The cardiac sounds were distant. A normal sinus rhythm was present, and no murmurs were heard. The abdomen was protuberant, soft and nontender, with a shifting dullness. No pelvic or abdominal masses were palpated. No rectal masses were palpated, and the feces were soft and yellow-brown. Two plus pedal and presacral edema was noted. The deep tendon reflexes were equal but hypoactive. No pathologic reflexes and no sensory or motor deficits were noted.

The urine was acid in reaction, with 3 plus albumin and numerous granular casts. The blood urea nitrogen level was 12 mg.%; blood glucose level, 65 mg.%; serum chloride level, 83 mEq./L.; serum CO<sub>2</sub> level, 31 mEq./L.; serum total protein, 4.5 gm.%, with albumin, 2.4, and globulin, 2.1 gm.%; serum direct bilirubin, 1.4 mg.%; indirect, 1.4 mg.%; prothrombin time, 36%. The 45-minute bromsulfalein retention was 33.5%. The electrocardiogram revealed low voltage and nonspecific ST changes, with a first degree heart block. The chest film showed a bilateral, miliary type of pulmonary infiltrate. The sputum, ascitic fluid and throat washings were negative for stained acid-fast bacilli. The intermediate PPD skin test was negative at 24 and 48 hours. The absolute eosinophil count was 73 per cubic millimeter. Three days after admission, the diagnosis of myxedema in addition to her undiagnosed pulmonary infiltrate was made. A serum protein-bound iodine level was reported as 2.6 µg.%. On May 17, daily intravenous administration was begun of 30 µg. of triiodothyronine in 500 c.c. of 5% dextrose in water. Procaine penicillin was instituted on an empiric basis for the lung infiltrate. The patient showed no improvement, and gradually deteriorated to a point where bed rails and tube feeding were required. Because of her critical condition, streptomycin and para-aminosalicylic acid were started on May 21, despite the inability to demonstrate acid-fast organisms on stained smear or culture. The patient was febrile at this time (101° F.), as she had been since admission. She became progressively more irrational and stuporous over the next several days. At no time was she significantly hypothermic. The lowest temperature recorded on the clinical thermometer was that of 97° F. rectally, on May 22 and 23, taken in the early morning hours. On May 23 she passed a dark stool mixed with fresh blood, and died shortly thereafter. Her vital signs a few minutes before death were: blood pressure, 92/70 mm. Hg; pulse, 88; respiration, 10.

At autopsy there were several ecchymotic lesions on the posterior surface of the upper and lower extremities. The abdominal cavity contained approximately 300 to 400 c.c. of clear, straw-colored fluid. All of the intraperitoneal structures were covered with small nodules of varying sizes. The pericardial sac contained approximately 50 c.c. of straw-colored fluid. The heart weighed 380 gm. and appeared to be normal. The coronary arteries were patent, with only minimal atherosclerosis. The aorta was markedly atherosclerotic. The larynx, trachea and bronchi were filled with a copious mucoid exudate. Both lung fields contained numerous small nodular areas. The hilar lymph nodes were enlarged and contained areas of caseous softening. The liver weighed 1,940 gm. and was pale on cut section. The spleen was not enlarged. Both organs had numerous small nodules on their surfaces. The kidneys, ureters and urine bladder were normal. The uterus was enlarged, and the uterus and Fallopian tubes had a large number of small nodules on their surfaces. The stomach was quite large and was filled with a yellow mucoid fluid. The entire bowel, distal to the ligament of Treitz, was filled with blood which appeared to rise from numerous bleeding points throughout the large and small bowel. The combined

adrenal weight was 19 gm. The adrenals appeared to be normal on external and cut surfaces. The cerebrum had numerous areas of caseous softening in both hemispheres and contained a large tuberculoma.

The stained sections revealed large numbers of tubercle bacilli in virtually every field examined. The thyroid was completely fibrotic, with only a few nests of cells resembling thyroid tissue remaining. A lymphocytic infiltrate surrounded by a chronic inflammatory reaction was present throughout the fibrotic remains of the gland. The thyroid lesion was not thought to be typical of any of the recognized forms of chronic thyroiditis. The adrenals were well preserved except for a typical caseous tubercle in the superior pole of the right adrenal. The liver showed a marked degree of fatty degeneration.

*Comment:* This patient appears to have died from miliary tuberculosis, but in addition she had severe myxedema. A complicating tuberculosis has long been noted to be present frequently in fatal myxedema.<sup>2</sup>

*Case 5.* A 60 year old white female with known hypertension and diabetes mellitus was admitted to the University Hospital on January 31, 1958, in congestive heart failure. She had had slight pedal edema and exertional dyspnea for four years. During the five-week period prior to admission she had experienced the onset of paroxysmal nocturnal dyspnea, and a progressive increase in pedal edema and exertional dyspnea. This had been refractory to a regimen of oral diuretics and digitalis instituted by her private physician. During the previous several weeks she had remained in her bed because she was "too heavy to move." She had had no recent or past chest pain. She was on no diabetic or antihypertensive regimen. For the last 20 years she had weighed in excess of 180 pounds. Her past history revealed weakness, fatigue and constipation for many years. She had noted a coarsening of her hair and drying of her skin for the last four years. Recently her speech had become slurred. Her menstrual periods had been irregular, with reduced flow, and menopause had occurred at age 50.

She was an obese, lethargic white female in chronic distress. Her blood pressure was 190/100 mm. Hg; pulse, 88; respiration, 20. The skin was dry, coarse and cool. Her hair was coarse and dry, and was thinly distributed in the axillary and pubic regions. There was periorbital and dependent edema. The optic fundi showed slight AV compression. Her tongue was thick, and her voice was deep and coarse. The thyroid was not palpable. The chest was clear except for an occasional moist râle at the bases. The point of maximal impulse was in the fifth to sixth intercostal space in the midclavicular line. No murmurs were heard, but an intermittent protodiastolic gallop rhythm was present. A hard, movable mass was palpated in the umbilical region, and a fluid wave was present, along with shifting flank dullness. The bowel sounds were normal. A rectocele and cystocele were present. The deep tendon reflexes were equal bilaterally and hypoactive, with a slow relaxation phase.

The blood urea nitrogen level was 10.5 mg.%; blood glucose level, 370 mg.%; and serum concentrations of the following were obtained: chloride, 77 mEq./L.; CO<sub>2</sub>, 25 mEq./L.; sodium, 130 mEq./L.; potassium, 2.7 mEq./L.; cholesterol, 262 mg.%; total lipids, 680 mg.%; calcium, 9.0 mg.%; phosphorus, 2.1 mg.%; total protein, 5.8 gm.%, with albumin, 3.6, and globulin, 2.2 gm.%. The white blood cell count was 14,750 per cubic millimeter, with a differential count of 16 lymphocytes, 7 monocytes, 76 neutrophils and 1 basophil. The hematocrit was 45%, and the sedimentation rate (Wintrobe) was 32 mm. per hour. The urine had a specific gravity of 1.014, 2 plus glucose, and 1 to 3 white blood cells per high power field, and was moderately positive for acetone.

On admission the patient was placed on digitalis, a sliding-scale insulin regimen,

and oral potassium. She became progressively more agitated, disoriented and uncooperative. Bed rails and arm restraints were required throughout most of her hospital course. On February 2, 1958, she was noted to have abdominal distention, and an abdominal film revealed gaseous distention of the stomach and colon. A Levine tube was passed and 750 c.c. of gastric fluid were withdrawn. The Levine tube was left in place, and for the next several days the patient received tube feeding and intermittent gastric suction. A bigeminal cardiac rhythm noted at this time was converted to a normal sinus rhythm after 1,000 c.c. of Ringer's lactate containing 20 mEq. of potassium were given intravenously. On February 4, 1958, a 24-hour radioiodine uptake was 7%. The serum protein-bound iodine level was 0.75  $\mu\text{g.}\%$ . Desiccated thyroid, 15 mg. daily, was started on February 6, 1958. The patient developed rales at both bases, associated with a temperature elevation to 100° F. Examination of the sputum revealed a moderate number of gram-positive diplococci. A urine culture had an abundant growth of *Escherichia coli*. Chloramphenicol, 250 mg. every six hours by mouth, and procaine penicillin, 600,000 units intramuscularly twice daily, were started. On February 7, 1958, the patient was quite difficult to awaken, and remained very lethargic during the rest of her hospital course. No sedatives had been given. She remained febrile and had expiratory wheezes bilaterally. She appeared to be in mild respiratory distress, and slight cyanosis of the lips was noted.

Her laboratory values at this time were: blood urea nitrogen level, 18.5 mg.%; serum  $\text{CO}_2$ , 30 mEq./L.; serum cholesterol level, 218 mg.%; white blood cell count, 12,500 per cubic millimeter, with a predominance of neutrophils. The lethargy was thought to be due to  $\text{CO}_2$  narcosis and myxedema. At this time (February 7), it was felt that a more vigorous approach to thyroid replacement should be attempted. The oral thyroid started the day before was discontinued, and 15  $\mu\text{g.}$  of triiodothyronine were given intravenously, along with 100 mg. of hydrocortisone in 1,000 c.c. of 5% dextrose in water. In addition, 100 mg. of cortisone were given intramuscularly. On February 8, 1958, the patient died quietly in bed. She was observed shortly before death and there was no apparent change in her condition. Her diabetes was never satisfactorily controlled, even though as much as 160 units of insulin was being given per 24 hours. At no time was she significantly hypothermic. The lowest oral temperature recorded was 97° F. Autopsy permission was not granted.

*Comment:* The cause of death was not apparent clinically. It was obvious that the intravenous triiodothyronine had little effect on the clinical picture. The administration of larger amounts of triiodothyronine would have been hazardous, because of her cardiac status. The association of diabetes mellitus and myxedema is somewhat unusual.<sup>36</sup>

#### DISCUSSION

The signs and symptoms characteristic of myxedema are insidious in onset and progression. If the disease is not treated, death follows a continued intensification of these signs and symptoms. The length of time from onset to death varies between 10 and 15 years.<sup>23</sup> In most cases, myxedema plays a predominant but indirect role in the development of the immediate cause of death, i.e., death due to pulmonary, cardiovascular or renal complications, or various combinations of these.<sup>2, 23</sup> This is the usual clinical course of the disease without replacement therapy. Some few cases,



TABLE 1—Summary of Reported Cases of Myxedema Coma

Reference	Age	Sex	Hours in Coma	Temp., °F.	Blood Pressure	Pulse	BUN, mg. %	Blood Sugar, mg. %	Serum Na <sup>+</sup> , mEq./L.	Serum K <sup>+</sup> , mEq./L.	Cholesterol, mg. %	Hemoglobin	BMR	PBI, gamma %	RAL, 24-hr.
3	59	M	96	83			40	110	140	5.6	180				
3	65	F	72	75	70/?	60	31	140	122	5.8	160	11.0*			
3	63	M	24	87.5	155/100	66	53	94	120	6.2	280				
3	59	M	24	96	130/75	64	48		132	5.7	310				
3	59	M	48	83.5	Not obtainable	75		85	135	6.0	560	14.25*			
4	70	F	48	74	Not obtainable	34	20								
5	60	F	34	95.2	130/90	54	36		112	3.2	242	112†			
5	64	F	20	78	140/100	40	14	75	134	4.2	308	78†			
5	62	F	48	<95	Not obtainable	40	60	93	Normal	5.8	538	13.5*			
5	67	F		80			30	102	118	3.5	390	90†			
6	61	F	96	97	140/100	62	50	57	150	4.7	495				
6	50	F	21	95	250/140	42	25		128						
7	49	M		84	Not obtainable	48									
8	63	F	24	99	obtainable	68	61		139	4.1	336	13.6*	-8%		4.5%
9	65	F	96	97	160/100		122		113		292	9.4*			10%
10	70	F	120	82	230/115	62	25	126	122	6.3	393	75†			
11	70	F	24	75.2	Not obtainable	Not obtainable		48	116	6.2	293	14.8*			
12	19	M	24	82	obtainable	50		100	144	6.7	200	98†			
12	80	F	80/60	91	80/60	50					280	60†			
12	79	F	12	91	95/?	60	44		152	5.1	200	84†			
13	41	F	48	97.2	100/?	65	NPN 20 mg. %	108	147	4.7	450	14*	-9%	1.2	
14	54	F	36	96.8	Not obtainable	48					680		-55%		11%
15	80	F	40	96	obtainable	60	Normal	Normal	115	3.9	326	9.5*		0.9	
Present series**	71	F	120	99	160/80	76	12.0	72	129	3.8	84	38 hematocrit		1.0	
	48	F	148	95.8	86/64	58	13	85	116	4.0	503	32 hematocrit		4.9	4%

\*\* Values shown are the lowest recorded during the period of coma.

† %.

\* gm. %.

however, deviate from this in that the complications play a definitely less important role, and death in a hypothermic coma follows a long history of hypothyroidism.

Myxedema coma has been recognized since the early days of thyroid investigation. In 1888 several cases were included in the Myxedema Report of the Clinical Society of London.<sup>2</sup> Since then, however, there have been only scattered reports and brief mention in the standard textbooks.<sup>23-27</sup> The clinical picture and its prevalence were not generally appreciated until 1953.<sup>3, 4</sup> The clinical data of 25 cases, including two from the present series are summarized in table 1. These patients have the characteristic physical and historical findings of myxedema. The average age has been 60 years; the only exception from this has been one juvenile case in coma. Females predominate over males in a ratio of 3:1. They may present in coma, or be extremely lethargic and later lapse into coma. A grand mal seizure has been observed in about 25% of the cases during the early phases of coma. Hypothermia has been a striking feature of the syndrome. All but one of the reported cases occurred during the winter months. Fifteen of the 25 summarized cases had a temperature below 95° F.; a low of 74° F. was recorded in one patient.<sup>6</sup> It is interesting that, despite the hypothermia, these patients did not shiver. The majority of the patients have sinus bradycardia. The blood pressure is variable: it has ranged from hypertensive to markedly hypotensive levels.

The laboratory values obtained in the cases have demonstrated a mild to moderate anemia. The blood urea nitrogen level was often elevated. The serum electrolytes were quite variable but, as a general rule, hyponatremia and hyperkalemia were present. In many cases these values were as severely deranged as those one sees in Addison's disease. It is of interest that, in the present series, two of the patients had low serum potassium levels. The low serum sodium concentration has been shown to occur despite an elevated total body sodium, and presumably is related to the binding of this cation in the tissue.<sup>28</sup> The serum cholesterol ranged from 160 to 680 mg.%, with only a few values below 250 mg.%. The blood glucose levels were generally in the normal range. A few patients had abnormally low levels which, when corrected, had no effect on the clinical picture.

The usual program for treating myxedema is to start the patient on small amounts of thyroid substance (15 mg.), and increase slowly by 15 mg. every two weeks to a normal physiologic replacement level of between 90 and 180 mg. of desiccated thyroid or its equivalent. This is usually successful, although a few patients must be maintained on suboptimal doses because of angina pectoris, congestive failure or excessive nervousness. Most patients do well, and often live out their expected life span. In sharp contrast, the patients in myxedema coma have had a mortality of over 80%. Of the 31 episodes of coma (30 cases), only five have survived.<sup>3, 5, 12, 16, 17</sup> Replacement therapy in patients with myxedema coma has varied from small

amounts of oral desiccated thyroid to large amounts of triiodothyronine or thyroxine given parenterally. Glucocorticoids were given to 13 of the cases, two were given desoxycorticosterone acetate, and one case received ACTH. Many of the patients were warmed by hot tub baths or electric blankets.

The clinical data of the patients who survived were analyzed in an attempt to discover in what ways they may have differed from those who died. One case was not actually in coma but in pre- or semicoma. None of the survivors had a temperature below 90° F., and the serum electrolytes, when studied, were only moderately abnormal. In some respects, therefore, these cases were not so severe as the fatal ones. Another significant factor was that, in several instances, thyroxine or triiodothyronine was administered parenterally. It should be noted, however, that several of the patients who died had similar clinical pictures and also received parenteral thyroid replacement therapy.

Included in the present series are five patients with well documented myxedema who demonstrated marked variability in their clinical course and mode of death. The last three cases, although severely myxedematous, died without responding to therapy, one from pulmonary tuberculosis, and the other two probably from cardiovascular complications. The first two patients had severe myxedema as the predominant disease process. Case 1 presented with florid myxedema of at least 10 years' duration. Her death followed belated replacement with small amounts of parenteral triiodothyronine. Although the lack of significant hypothermia is not typical, several reported cases have not had this finding.<sup>6, 13</sup> Case 2, who was in semicoma, had a remarkable response to parenteral triiodothyronine. This patient, who developed myxedema stupor associated with hypothermia during the summer months, is the second such case reported.<sup>3</sup> Although a comparison of the patient's temperature with that of her environment suggests a correlation, there is no consistent relationship (figure 1). Gastrointestinal complaints, seen in two of the presently reported cases, are not unusual.<sup>24</sup> Such a clinical picture is characterized by increasingly severe constipation and progressive abdominal distention. Defecation is often absent for periods up to a week, with only rare passage of flatus. Paralytic ileus is relatively common, and acquired megacolon is almost uniformly observed, either radiologically or at autopsy. Case 1 was operated upon for symptoms related to acquired megacolon. The treatment of this complication should be conservative management with saline enemas, intubation if ileus is present, and thyroid replacement therapy. Although low serum cholesterol levels in case 1 are suggestive of pituitary myxedema, they could equally well be related to severe dietary restriction and malabsorption imposed by her obstipation.

The skeletal muscle changes demonstrated in case 2 have been seen occasionally in patients with myxedema,<sup>11, 27</sup> and similar lesions occur in

cardiac muscle, and in the smooth muscle of the gastrointestinal tract and vascular system.<sup>34, 35, 38, 39</sup> The disability in case 2 suggests a possible cause-and-effect relationship between prolonged hypothyroidism and muscle damage.

It has been shown in experimental animals that body temperature maintenance is thyroxine-dependent at low environmental temperatures,<sup>29, 30</sup> that one can quantitate the increase in the minimal thyroxine requirement as the environmental temperature is lowered,<sup>31</sup> and that death occurred in thyroidectomized rats maintained at moderate temperatures (16° C.) while on sub-optimal replacement therapy.<sup>31</sup> The death of these animals occurred from within several hours to two days, and was preceded by a progressive paralysis, drop in body temperature, and coma. At any stage, however, they would recover if placed in a warm environment (27° C.). In many respects the syndrome produced in these animals resembles that of myxedema coma in man. However, recovery of these animals after warming is in sharp contrast to the response of patients with myxedema coma treated similarly, and is probably related to the acute nature of the animal experiments, as compared to the chronic nature of the syndrome in man.

It has been shown that a small yet significant amount of thyroxine is contained in animal tissues which are commonly used for food sources,<sup>31</sup> and also that *in vivo* extrathyroidal synthesis of thyroxine may take place.<sup>32</sup> In addition, it has been suggested that inorganic iodides may iodinate various ingested proteins in the gastrointestinal tract and supply a small amount of thyroxine and less active iodinated compounds for body utilization.<sup>33</sup> The lack of these extrathyroidal thyroactive substances may have contributed to the clinical picture in cases 1 and 3, who had severe gastrointestinal symptoms and whose histories indicated self-imposed dietary restrictions.

Patients with myxedema show varying combinations of both metabolic and secondary anatomic defects. In patients with predominantly metabolic defects, such as myxedema coma and hypothermia, the treatment should be that of immediate replacement with a thyroactive substance. The parenteral route of administration is desirable because of the possibility of poor intestinal absorption of an orally administered preparation. Triiodothyronine has the advantage of rapid onset of action (within several hours). The dose should be highly individualized, and titrated with the clinical response of the patient. If the patient shows no response to small or physiologic amounts of triiodothyronine (10 to 100 µg. daily), the amount administered should be progressively increased. Although these recommendations are quite different from the usual methods of treating patients with myxedema, they are prompted by the high mortality of patients with myxedema coma treated with the presently accepted therapeutic regimen, and the successful outcome of several cases treated parenterally with large amounts of thyroactive substances.

In the usual patient with myxedema whose clinical picture is dominated

by secondary (pathologic) conditions, such as congestive heart failure, anemia, and intestinal paresis, and who does not appear to be in immediate danger of lapsing into stupor or coma, the treatment is much more conservative. Triiodothyronine in doses of 5 to 12.5  $\mu$ g., or desiccated thyroid in doses of 15 mg. daily, should be given orally. This should be increased at two-week intervals as tolerated by the patient. If at any point angina pectoris or congestive heart failure develops, the dose should be reduced immediately to the previous level. The presence of congestive heart failure is by no means a contraindication to initiation of therapy, since many of these patients are in congestive failure secondary to the cardiac lesions of myxedema, and thyroid replacement therapy is the treatment of choice.<sup>40</sup>

The value of glucocorticoids in myxedema coma has not been demonstrated. Early reports based on decreased urinary excretion of 17-ketosteroids<sup>41, 42</sup> and 17-hydroxycorticosteroids,<sup>43</sup> and the failure of exogenous ACTH to produce a fall in circulatory eosinophils, indicated an impaired adrenocortical function in patients with myxedema. A more recent study has demonstrated a normal plasma 17-hydroxycorticosteroid level and an adequate response to exogenous ACTH, and has also shown that the decreased urinary excretion of 17-hydroxycorticosteroids was due to their decreased metabolism in patients with myxedema.<sup>44</sup> However, it has not been demonstrated that a "myxedematous" pituitary can rapidly increase its secretion of ACTH in response to sudden stress. The fact that urinary gonadotropins are decreased in these patients and return to normal with thyroid therapy indicates some decreased pituitary activity.<sup>45</sup> Patients with primary panhypopituitarism often present with myxedema dominating the clinical picture, and these patients may also develop a hypothermic coma.<sup>46, 47</sup> The differentiation of panhypopituitary coma from the coma of primary thyroid atrophy (myxedema coma) can seldom be readily made at the bedside. A varying degree of impaired pituitary-adrenal responsiveness may therefore be present, and it is felt that glucocorticoids are physiologically indicated. Because of the detrimental effect of large amounts of a thyroactive compound in adrenal insufficiency, the administration of glucocorticoids in hypothermic coma is even more advisable.

The application of heat to the severely hypothermic patient has been of apparent value in some of the reported cases, but in most no change in the clinical picture has occurred. However, unless definite contraindications are demonstrated, these patients should continue to have their body temperatures gradually elevated to a normal or near-normal level.

Even with a vigorous approach to therapy, the mortality in myxedema coma will probably remain high. The ideal treatment of these patients is early recognition of their condition, and replacement with thyroid hormone before this discouraging late clinical picture appears. Although fatal myxedema and myxedema coma are certainly more prevalent than generally considered to be the case, the high incidence of five such patients in two

years may also be a reflection of the low socio-economic status of the indigent-patient group from whom these cases were drawn.

#### SUMMARY

1. Myxedema is a potentially fatal disease. In most untreated patients, death is due to cardiovascular, pulmonary or renal complications. A few patients, however, die in a hypothermic coma.

2. In the present series, five patients with severe myxedema are presented: four died without responding to replacement therapy, and one, in semicoma, recovered with therapy. One patient died in coma.

3. The therapy of myxedema coma in the present and previously reported cases has been unsatisfactory. A few patients, including one in the present series, have responded to relatively large doses of parenterally administered thyroxine or triiodothyronine. Intravenous triiodothyronine in individualized doses appears to be the treatment of choice.

4. The value of glucocorticoids and heat in myxedema coma has not been clearly demonstrated. Their use is rational, and they should be continued until there are definite contraindications.

#### ADDENDUM

A significant report which is pertinent to the present discussion has recently appeared: Nordqvist, P., Dhuner, K.-G., Stenberg, K., and Orndahl, G.: Myxoedema coma and CO<sub>2</sub>-retention, *Acta med. scandinav.* **166**: 189, 1960.

This paper presents data which suggest that some of the features of myxedema coma are due to CO<sub>2</sub> narcosis. The elevated serum CO<sub>2</sub> levels noted in cases 2, 3, 4 and 5 of the present report would favor such a conclusion and emphasize the necessity for considering prolonged artificial respiration in other similar patients.

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#### SUMMARY IN INTERLINGUA

Ben que myxedema mortal e coma per myxedema esseva descripte al tempore del prime investigationes del thyroide, in le annos subsequente illos recipeva pauc attention usque recentemente un trentena de casos esseva publicate. Iste patientes ha un apparentia characteristicamente myxedematose. In le casuistica publicate le etate medie del patientes esseva 60 annos. Femininas ha predominare. Tal patientes es presentate in coma o in stato de lethargia sever. Hypothermia ha essite un aspecto frappante del syndrome. In le majoritate del patientes le temperature esseva infra 95 F, e omne le casos—con un sol exception—occurreva durante le menses del hiberno. Le diagnose definitive depende frequentemente de basse nivellos de iodo ligate a proteina in le sero o del fixation de iodo radioactive per le thyroide. Le



anormalitates laboratorial notate le plus frequentemente—a parte illos relationate al function thyroide—eseva hyponatriemia e hyperkaliemia. Le mortalitate in coma myxedematose ha essite plus que 80%. Therapia substitutive ha utilisate variemente micre quantitates de thyroide desiccate o, al altere extremo, grande quantitates parenteral de triiodothyronina o thyroxina. Le superviventes eseva generalmente le patientes con disturbance minis sever de electrolyto e de temperatura e illes recipiente doses parenteral de substantias thyroide.

Le frequentia del occurrentia de iste complication es sublineate per le observation de cinque patientes con myxedema sever in le curso del passate tres annos. Solmente un de illes respondeva al mesuras de therapia substitutive. In omne iste casos, le patientes eseva feminas de etate plus tosto avantiate, con longe antecedentes de myxedema. Un del patientes comatose moriva sin signo de responsa al substitution terminal per micre quantitates parenteral de triiodothyronina. Le sol supervivente in iste serie deveniva hypothermic e glissava a in un stato semicomatose durante le menses del estate. Illa manifestava un marcate responsa a relativamente forte doses parenteral de triiodothyronina. Le remanente patientes, ben que severmente myxedematose, haveva concomitante processos pathologic como causa immediate del morte. Therapia substitutive con micre doses parenteral de triiodothyronina o de thyroide desiccate haveva nulle effecto super le stato clinic.

Le uso de triiodothyronina parenteral es recommendate in iste patientes. Si le patiente non responde a micre doses, le quantitate administrate deberea esser augmentate progressive- e rapidamente. Ben que un numero de patientes ha recipite glucocorticoides sin demonstrabile effectos benefic, le uso de glucocorticoides remane logic e debe esser continuate usque definite contraindicationes es trovate.

#### BIBLIOGRAPHY

1. Ord, W. M.: Cases of myxedema, *Tr. Clin. Soc. London* 13: 15, 1879-1880.
2. Report of a Committee of the Clinical Society of London to investigate the subject of myxedema, Supplement to Vol. 21 of the Clinical Society's Transactions, 1888, Longmans, Green & Co., London.
3. Summers, V. K.: Myxoedema coma, *Brit. M. J.* 2: 366, 1953.
4. Le Marquand, H. S., Hausmann, W., and Hemsted, E. H.: Myxoedema as a cause of death, *Brit. M. J.* 1: 704, 1953.
5. Malden, M.: Hypothermic coma in myxoedema, *Brit. M. J.* 2: 764, 1955.
6. Le Marquand, H. S., Hausmann, W., and Hemsted, E. H.: Death in myxoedema coma, *Brit. M. J.* 2: 773, 1955.
7. Andersen, A., and Hausmann, W.: Triiodothyronine in myxoedema coma, *Lancet* 2: 999, 1956.
8. Karhausen, L., and Zylberszac, S.: Myxoedema coma in a patient with Hashimoto's struma, *Brit. M. J.* 2: 766, 1955.
9. Knyvett, A. F., and Steinbeck, A. W.: A case of myxoedema coma, *M. J. Australia* 1: 722, 1957.
10. Dyson, A., and Wood, M. W.: Triiodothyronine in myxoedema coma, *Lancet* 2: 757, 1956.
11. Marshall, R. J., and McCaughey, W. T.: Hypothermic myxoedema coma with muscle damage and acute renal tubular necrosis, *Lancet* 2: 754, 1956.
12. MacDonald, D. W.: Hypothermic myxoedema coma. Three case reports, *Brit. M. J.* 2: 1144, 1958.
13. Levin, M. E., and Daughaday, W. H.: Fatal coma due to myxedema, *Am. J. Med.* 18: 1017, 1955.
14. Klotz, H. P., Avril, J., and Lumbroso, P.: A propos d'un coma myxoedemateux, *Ann. d'endocrinol.* 15: 300, 1954.

15. Kelly, J. J., and Sherk, H. H.: Myxedema coma, *Ann. Int. Med.* **50**: 1303, 1959.
16. Martin, L., and Whittle, C.: Myxoedema as a cause of death, *Brit. M. J.* **1**: 1108, 1953.
17. Brotmacher, L., and Coghill, N. F.: Myxoedema coma, *Brit. M. J.* **2**: 886, 1953.
18. Perrault, M., Klotz, B., and Willocher, B.: Coma myxoedemateux, *Semaine d. hôp. Paris* **32**: 495, 1956.
19. Biemond, A.: Sur le coma myxoedemateux, *Fol. psychiat. neurol. et neurochir. neerl.* **58**: 217, 1955.
20. Saric, R., Riviere, J., and Hui-Bon-Hoa, J.: A propos d'un observation de coma myxoedemateux, *J. de méd. de Bordeaux* **134**: 499, 1957.
21. Enger, E.: Precoma ved myxedem: meddelelse om et tilfelle, *Tijdschr. f. d. norske Lægefor.* **77**: 464, 1957.
22. Brown, H., Reingold, A. M., and Samson, M.: The determination of protein-bound iodine by dry ashing, *J. Clin. Endocrinol. and Metabolism* **13**: 444, 1953.
23. Means, J. H.: The thyroid and its diseases, 2nd Ed., 1948, J. B. Lippincott Co., Philadelphia.
24. Bastenie, P. A.: Paralytic ileus in severe hypothyroidism, *Lancet* **1**: 413, 1946.
25. Labbe, M.: Coma et myxoedeme, *Rev. gén. de clin. et de thérap.* **49**: 52, 1935.
26. Hertoghe, M.: On coma due to myxoedema, *Am. J. Ophth.* **28**: 140, 1911.
27. Watney, H. A., and Douthwaite, A. H.: A case of spontaneous acute myxoedema, *Brit. M. J.* **2**: 1142, 1932.
28. Aikawa, J. K.: The nature of myxedema: alterations in the serum electrolyte concentrations and radiosodium space and in the exchangeable sodium and potassium contents, *Ann. Int. Med.* **44**: 30, 1956.
29. Bodansky, M., and Duff, V. B.: Nitrogen and creatine metabolism in relation to environmental temperature and thyroid function, *Endocrinology* **20**: 822, 1936.
30. Bodansky, M., Pilcher, J. E., and Duff, V. B.: Concerning the relationship to environmental temperature to resistance to thyroid and thyroxine and creatine content of heart and other tissues in experimental hypothyroidism, *J. Exper. Med.* **63**: 523, 1936.
31. Leblond, C. P., and Eartly, H.: An attempt to produce complete thyroxine deficiency in the rat, *Endocrinology* **51**: 26, 1952.
32. Morton, M. E., Chaikoff, I. L., Reinhardt, W. O., and Anderson, E.: Radioactive iodine as indicator of metabolism of iodine; formations of thyroxine and diiodotyrosine by completely thyroidectomized animals, *J. Biol. Chem.* **147**: 757, 1943.
33. Leblond, C. P.: Fate of iodine in the body, *J. Am. Pharm. A. (Scient. Ed.)* **40**: 595, 1951.
34. Douglass, R. C., and Jacobson, S. D.: Pathologic changes in adult myxedema: survey of 10 necropsies, *J. Clin. Endocrinol. and Metabolism* **17**: 1354, 1957.
35. Berkheiser, S. W.: Adult hypothyroidism: report of an advanced case with autopsy study, *J. Clin. Endocrinol. and Metabolism* **15**: 44, 1955.
36. Carey, J. B., Arey, S. L., and Norris, E. H.: Myxedema and diabetes mellitus; a case report with autopsy findings, *Ann. Int. Med.* **11**: 838, 1937.
37. Foster, M., and Ban, D.: Myxedema; record of an autopsied case with special emphasis upon lesions of muscles, *J. Clin. Endocrinol.* **4**: 417, 1944.
38. Higgins, W. H.: The heart in myxedema: correlation of physical and post mortem findings, *Am. J. M. Sc.* **191**: 80, 1936.
39. LaDue, J. S.: Myxedema heart: a pathological and therapeutic study, *Ann. Int. Med.* **18**: 332, 1943.
40. McGavack, T. H., and Schwimmer, D.: Problems in the treatment of cardiac failure in myxedema, *J. Clin. Endocrinol.* **4**: 47, 1944.
41. Statland, H., and Lerman, J.: Function of the adrenal cortex in myxedema, with some observations on pituitary function, *J. Clin. Endocrinol.* **10**: 1401, 1950.

42. Hill, S. R., Jr., Reiss, R. S., Forsham, P. H., and Thorn, G. W.: The effect of adrenocorticotropin and cortisone on thyroid function: thyroid-adrenocortical interrelationships, *J. Clin. Endocrinol.* **10**: 1375, 1950.
43. Levin, M. E., and Daughaday, W. H.: The influence of the thyroid on adrenocortical function, *J. Clin. Endocrinol. and Metabolism* **15**: 1499, 1955.
44. Williams, G. A., Crispell, K. R., and Parson, W.: Adrenocortical function in myxedema, *J. Clin. Endocrinol. and Metabolism* **17**: 1347, 1957.
45. Beierwaltes, W. H., and Bishop, R. C.: 17-ketosteroid and pituitary follicle-stimulating hormone excretion in myxedema, before and during treatment with thyroxine, *J. Clin. Endocrinol. and Metabolism* **14**: 928, 1954.
46. Sheehan, H. L., and Summers, V. K.: Treatment of hypopituitary coma, *Brit. M. J.* **1**: 1214, 1952.
47. Sheehan, H. L., and Summers, V. K.: Syndrome of hypopituitarism, *Quart. J. Med.* **18**: 319, 1949.

## PERICARDIAL DISEASE COMPLICATING CON- GENITAL HEART LESIONS \*

By HERBERT J. SEMLER, M.D., ROBERT O. BRANDENBURG, M.D., F.A.C.P.,  
and JOHN W. KIRKLIN, M.D., *Rochester, Minnesota*

PERICARDIAL disease superimposed upon a congenital intracardiac defect may, if unrecognized, simulate right heart failure, and hence suggest a very high surgical risk. It is important to identify the coexistence of both conditions, since they are usually correctable by present-day surgical technics.

Pericardial disease complicating congenital malformations of the heart has rarely been reported. Taussig<sup>1</sup> described the pathologic findings in a nine year old girl (case 35) who, it was thought clinically, probably had an "auricular septal defect and a superimposed rheumatic infection." Necropsy revealed unsuspected fibrinous pericarditis, with 150 c.c. of pericardial fluid, in association with an atrial septal defect, mitral stenosis and lobular pneumonia. Further review of the medical literature disclosed only isolated reports of the two conditions occurring together.<sup>2,3</sup> In a report on 60 patients with chronic constrictive pericarditis, White<sup>4</sup> mentioned having seen one patient with a coexistent congenital septal defect. In the various classifications of pericardial disease presented in textbooks on heart disease,<sup>5-7</sup> none was found that included instances of congenital intracardiac defects.

### MATERIAL AND METHOD

Pericardial disease in association with a congenital intracardiac lesion was diagnosed in six patients seen at the Mayo Clinic from April 1, 1954, through August, 1959. All had cardiac catheterization and subsequent surgical correction of their cardiac lesions. The combination of the two conditions resulted in problems of diagnosis and treatment not usually encountered. Hence, the clinical and surgical experience gained from these patients forms the basis of this report.

There were four women and two men, ranging in age from 17 to 48 years. All had a transatrial shunt except case 4, who had pulmonary stenosis with intact atrial and ventricular septa (table 1). This shunt was associated in cases 1, 2 and 3 with either constrictive or fibrinous pericarditis, whereas in cases 4, 5 and 6 a large pericardial effusion coexisted. Prior to operation, cardiac catheterization was performed using technics described previously.<sup>8,9</sup>

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From the Sections of Medicine and Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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TABLE 1  
Diagnosis at Operation

Case	Age (years), Sex	Diagnosis*
1	17 M	ASD; chronic constrictive pericarditis
2	31 F	Anomalous venous connection from right lung to inferior vena cava; valvular-competent, patent foramen ovale; fibrinous pericarditis and pericardial effusion (300 c.c.)
3	33 M	ASD; tricuspid insufficiency; chronic constrictive pericarditis
4	41 F	Pulmonic stenosis; pericardial effusion (1,200 c.c.)†
5	47 F	ASD; pericardial effusion (1,000 c.c.)‡
6	48 F	ASD; pulmonary hypertension; pericardial effusion (1,500 c.c.)

\* ASD = atrial septal defect.

† Plus preoperative pericardiocentesis of 1,200 c.c.

‡ Plus preoperative pericardiocentesis of 200 c.c.

## CASE REPORTS

*Case 1.* A 17 year old youth was referred to the Mayo Clinic because of uncontrolled ascites in association with a congenital heart defect. He was known to have had a cardiac murmur since the age of five, and his activities had remained unlimited until he was 14 years old, when progressive exertional dyspnea appeared. Two years later he was hospitalized after an accidental exposure to carbon tetrachloride, which was followed by fever, a generalized seizure and subsequent ascites. Despite multiple paracenteses, the ascites recurred frequently during the ensuing 15 months. Abdominal exploration elsewhere had revealed a thickened peritoneum, and biopsy of the liver had been interpreted as disclosing "cirrhosis."

On examination, the patient appeared to be chronically ill. The blood pressure was 95/60 mm. Hg in the right arm, and 105/80 mm. Hg in the left arm. Jugular veins were distended 5 cm. above the clavicle when the patient was recumbent. He had moderate dorsal scoliosis. A systolic murmur of grade 2 intensity (graded on a basis of 1 to 4) was heard over most of the precordium, being loudest in the left second and third intercostal spaces close to the sternum. The second sound in the left second interspace was accentuated (grade 2), and diastole was clear. The patient had marked ascites and a tender, enlarged liver.

Laboratory studies revealed normal hemoglobin concentration, erythrocyte count, sedimentation rate and urinary findings. Other data were: blood urea, 42 mg. per 100 c.c.; bilirubin, direct negative and indirect, 1.4 mg. per 100 c.c.; prothrombin time, 24 seconds; serum sodium, 122; serum potassium, 5.1; plasma chlorides, 80; plasma carbon dioxide-combining power, 15.8 mEq./L.; serum albumin, 3.61 gm., and serum globulin, 2.01 gm. per 100 c.c.; tuberculin skin reaction, negative.

An electrocardiogram showed low amplitude of the QRS complexes and right bundle branch block (figure 1a). X-ray examination revealed moderate enlargement of the cardiac silhouette, with moderate increase in the pulmonary vascular markings (figure 2a).

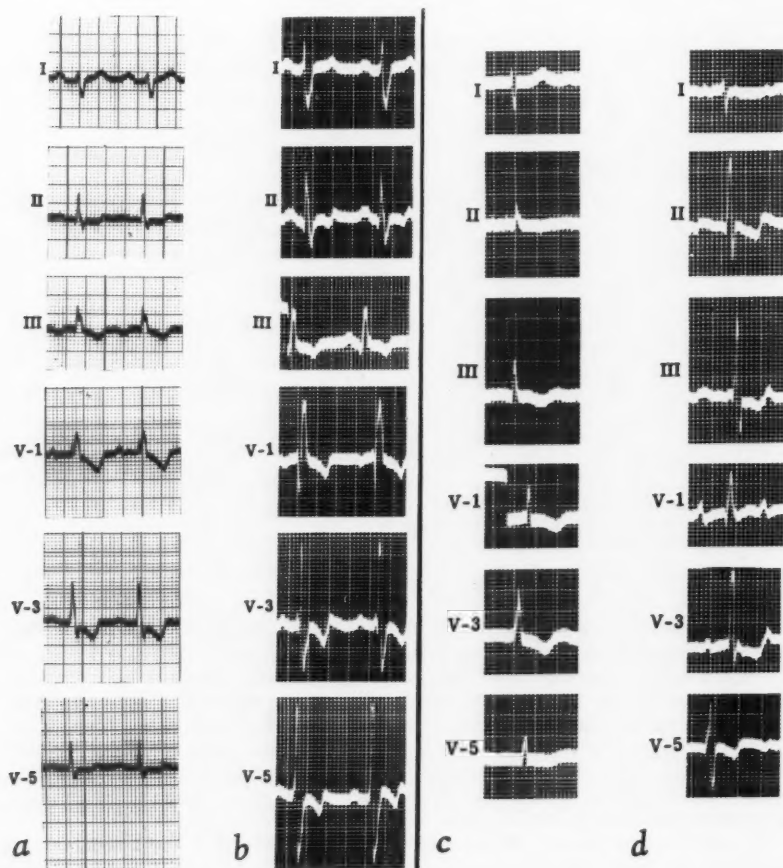


FIG. 1. *a* and *b*. Cases 1 and 3. Electrocardiograms of two patients, each of whom had an atrial septal defect and constrictive pericarditis. *c* and *d*. Cases 4 and 6. Electrocardiograms of two patients, each of whom had a large pericardial effusion associated with an atrial septal defect and right ventricular hypertension. Note difference in amplitude of QRS complexes between A and B, and between C and D.

Cardiac catheterization demonstrated a left-to-right shunt at the atrial level, associated with a left superior vena cava and moderate increase of right atrial and right ventricular pressure (table 2). The pressure contour of the right ventricle showed an early diastolic dip, followed by a diastolic plateau compatible with impaired filling of the ventricle. Two days later, thrombophlebitis of the right axillary vein appeared, requiring anticoagulant therapy. At this time a friction rub accompanied by a "paradoxical" pulse was audible over the lower sternal area. Because of the likelihood of constrictive pericarditis complicating the atrial septal defect, pericardial exploration was performed, which revealed a constricting peel on the surface of the two ventricles. Following decortication of the pericardium, the surgeon noted



TABLE 2

Cardiac Catheterization Findings in Patients with Pericardial Disease Complicating Congenital Heart Lesions (Patients Breathing Room Air)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, Sex	17, M	31, F	33, M	41, F	47, F	48, F
Body surface area, sq. meters	1.9	1.6	1.8	1.7	1.6	1.6
Pressure, S/D in mm. of Hg						
Brachial vein	25/21	22/18	15/6	23 (Mean)	13/4	20/18
Right atrium	27/22	26/16	17/7	30/20	13/5	23/14
Right ventricle	41/15-25*	47/20*	50/3-18	228/18-25	38/6-11	127/9
Pulmonary artery	51/31	55/30	46/20	20/13	38/12	114/39
Pulmonary artery "wedge"	26/21*	27/20	19/10	—	18/13	—
Left atrium	26/20	—	18/9	—	16/10†	22/14
Systemic artery	106/62	116/80	123/74	106/62	128/74	101/74
Oxygen saturation of blood, per cent						
Mixed venous‡	57	75	66	58	78	65
Right atrium	85	90	87	52	96	87
Right ventricle	—	—	88	61	93	88
Pulmonary artery	77	87	89	56	93	88
Systemic artery	96	96	96	93	97	95
Blood flow, L./min./M <sup>2</sup>						
Pulmonary	3.5	9.6	9.0	1.9	18.4	8.1
Systemic	1.9	4.8	2.6	(No shunt)	4.1	2.5
Resistance, dynes sec. cm. <sup>-5</sup>						
Total pulmonary	480	195	155	360	60	390
Systemic	1,680	955	1,700	1,850	1,070	1,660
L-R shunt, per cent of pulmonary flow	46	46	66	0	75	75

\* While breathing 99.6% oxygen.

† Pulmonary vein.

‡ Obtained from sum of oxygen saturation of the blood in superior vena cava and that in inferior vena cava, divided by two.

improved action of the heart. The postoperative course was uneventful and the ascites disappeared. Nine months later the atrial septal defect was repaired by means of the atrial-well technic by Dr. JDMortensen, of Salt Lake City, who kindly informed us of the operative findings and the patient's subsequent favorable course.

*Case 2.* A 31 year old housewife came to the Mayo Clinic initially on February 29, 1944, for a general examination. "Leakage of the heart" had been known since the age of 18 years, following a "flu-like illness." She had no history suggestive of rheumatic fever or repeated streptococcal infections. She was asymptomatic, and her blood pressure was 120/100 mm. of Hg. The second sound in the left second interspace was slightly accentuated. A systolic murmur was heard at the apex. Roentgenograms showed cardiac enlargement and pulmonary vascular congestion. An electrocardiogram disclosed right axis deviation. The hemoglobin concentration, erythrocyte and leukocyte counts, urinary findings and sedimentation rate were normal.

In 1946, the patient had an uncomplicated pregnancy.

She returned on November 9, 1953, and was admitted to the hospital. Her main complaint was retrosternal pain, described as a "tightness" in the region under the xiphisternum. This had recurred continuously during the preceding month, and was accentuated by exertion and relieved partially by rest. Her distress was considered to be related to an enlarged, congested liver. Orthopnea and paroxysmal nocturnal dyspnea had not occurred.

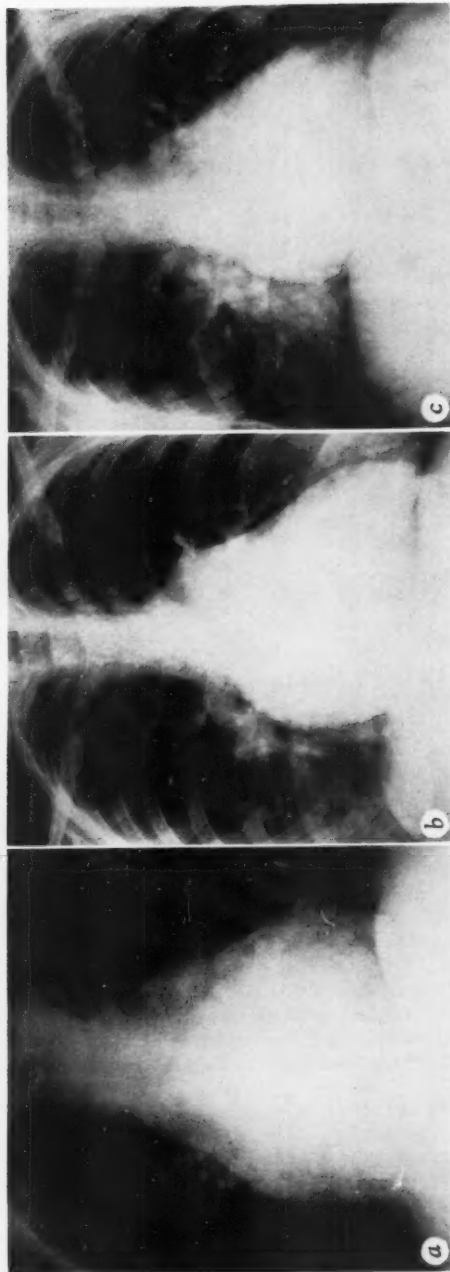


FIG. 2. *a* to *f*. Posteroanterior roentgenograms of the thorax in cases 1 to 6, respectively. Diffuse enlargement of the cardiac silhouette is uniformly present in all cases, as described in the text.

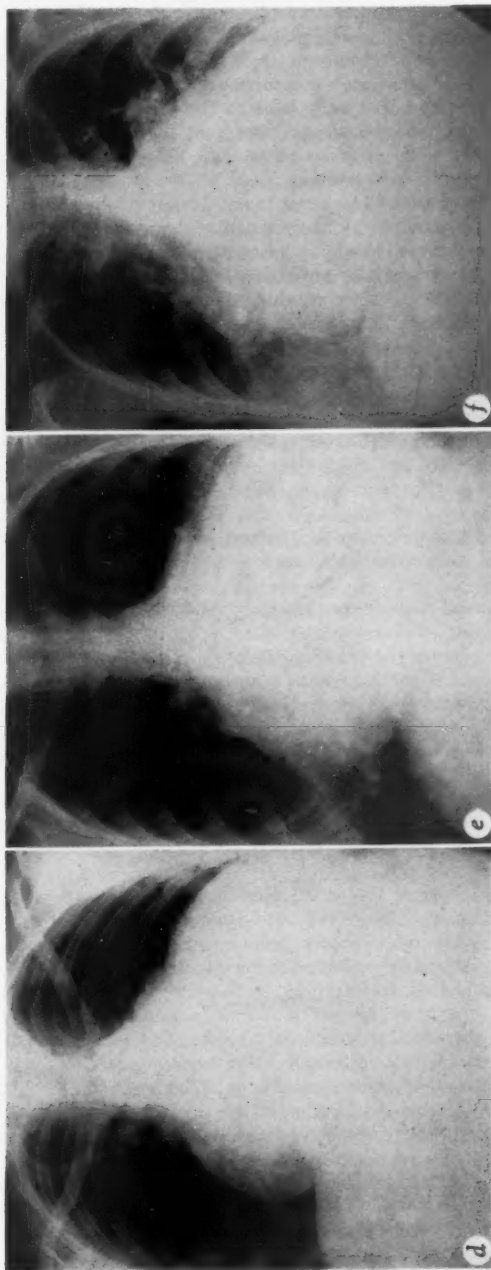


FIG. 2—Continued

Examination revealed a well nourished woman who was mildly dyspneic. The blood pressure was 136/90 mm. of Hg, and the pulse rate was 110 per minute. There was no cyanosis or clubbing. A strong systolic pulsation was palpable on the left side of the sternum. The pulmonary component of the second sound was louder than the aortic. The first sound was very loud at the apex. A soft, grade 1 systolic murmur was heard along the left sternal border in the second and third intercostal spaces, extending into the left infraclavicular area. Hepatomegaly was accompanied by tenderness in the right upper quadrant.

An electrocardiogram showed right axis deviation, incomplete right bundle branch block and questionable right ventricular hypertrophy. A roentgenogram revealed cardiac enlargement, involving principally the right ventricle (figure 2b). The pulmonary artery segment was prominent and the pulmonary vascular markings were increased. A tubular shadow passing vertically along the right hilar region suggested the possibility of an anomalous pulmonary vein. Fluoroscopy revealed marked enlargement of the cardiac silhouette, with probable hypertrophy of both ventricles, and no evidence of left atrial enlargement. Hilar vascular shadows were enlarged but pulsations were not exaggerated.

The value for hemoglobin was 9.4 gm. per 100 c.c., and the leukocyte count was 4,900 per cubic millimeter. Urinalysis gave negative results. A peripheral blood smear showed anisocytosis and mild hypochromasia. Blood cultures, sedimentation rate, and concentrations of protein-bound iodine, serum bilirubin and blood urea were all normal or negative.

Cardiac catheterization revealed arterialization at the atrial level, and there was a question of partial anomalous pulmonary venous connection from the right lung (table 2).

The patient showed a poor response to anticongestive therapy. She became apathetic and depressed, and returned home for a few weeks.

Reevaluation on January 12, 1954, disclosed a grade 3, to-and-fro pericardial friction rub, audible over the precordium and accompanied by a palpable systolic friction impulse. Venous pressure was slightly increased, and the liver had decreased in size. The possibility of a pericardial effusion was suggested, and the patient was therefore rehospitalized. Laboratory findings were: hemoglobin, 11.6 gm.; sedimentation rate, 77 to 86 mm.; blood urea, 14 mg.; tuberculin skin reaction, negative. There were no lupus erythematosus cells in the peripheral blood, and serum agglutination studies were negative for *Brucella*. Fluoroscopy showed marked cardiac enlargement and pulmonary vascular congestion. The amplitude of cardiac pulsations was slightly reduced.

On January 27, biopsy of the pericardium showed "fibrinous pericarditis." Approximately 300 c.c. of fluid were removed from the pericardial space. Cytologic study of this fluid disclosed no malignant cells. Cultures of the tissue and fluid from the pericardium were negative for acid-fast bacilli, *Brucella* and fungi.

The patient returned on July 6, 1954, feeling quite well. The physical findings were essentially the same as on the previous examination. Jugular venous pulsations were grade 2, and peripheral edema was absent. Cardiac catheterization showed evidence of anomalous drainage of the right pulmonary veins into the right atrium, associated with a 46% left-to-right shunt at the atrial level.

On July 29, thoracotomy disclosed a rather thick, congenital pleural fold along the greater fissure, so that the right lower lobe was actually in a completely separate pleural compartment. There was an old adhesive pericarditis. A single large venous trunk was found into which emptied the veins from the upper, middle and lower lobes of the right lung. This main trunk formed about 4 cm. above the diaphragm, and then pierced the diaphragm to enter the inferior vena cava just below the diaphragm. An interatrial communication, measuring 2.5 by 2 cm., was present

and considered anatomically as a valvular-competent, patent foramen ovale facing into the inferior vena cava. The anomalous vein was disconnected from the inferior vena cava and reimplanted into the left atrium, following which the interatrial communication was closed.

The patient had an uneventful postoperative recovery, and subsequent annual examinations disclosed that her cardiovascular status remained excellent and that she required no cardiac drugs. A roentgenogram revealed no significant cardiac enlargement or pulmonary vascular congestion. Four years later the patient had a normal, full term pregnancy, and appeared to be well when seen in October, 1959.

*Case 3.* A 33 year old male laborer was referred initially on September 18, 1953, for cardiac evaluation. He had had a normal birth and development, without any history of cyanosis, orthopnea, nocturnal dyspnea or rheumatic fever. A heart murmur was first heard when he was about 12 years old. His activities remained unlimited until 1948, when he consulted his physician because of episodes of dizziness, nervousness and sweating. He never lost consciousness. An episode of subacute bacterial endocarditis had followed an upper respiratory infection in 1949. His temperature reached 104 to 105° F., and he received "128 penicillin injections" during a five-week hospitalization elsewhere. The etiologic organisms were not known.

When the patient was examined at the Mayo Clinic he actually felt rather well, and presented no apparent real disability. Mild dyspnea and fatigue occurred after climbing one and a half flights of stairs or walking two or three blocks.

The blood pressure was 114/70 mm. of Hg in both arms. No clubbing or cyanosis was evident. A grade 2, harsh systolic murmur, obscuring the first sound, was heard loudest inside the apex, and was transmitted better toward the xiphoid than toward the axilla when the patient was supine. The second sound in the left second intercostal space was nearly normal, and no diastolic murmur was heard.

Laboratory data disclosed no significant abnormalities. An electrocardiogram revealed right bundle branch block and probable right ventricular hypertrophy (figure 1b). The T waves were inverted in Leads II, III and V-1 through V-5. X-ray examination revealed cardiac enlargement, with fullness in the pulmonary artery segment, enlargement of the main pulmonary vessels, and marked increase in pulmonary vascular markings (figure 2c). Cardiac catheterization disclosed arterialization at the atrial level, with a question of associated tricuspid insufficiency (table 2). Because of the possibility that this represented a partial atrioventricular-cushion type of defect, surgical treatment was considered best deferred until further refinements in technics were available.

The patient's condition was reevaluated in April and in July, 1956. He continued to feel generally well. He required no cardiac drugs or dietary restrictions. The findings were essentially the same as previously except that there now was evidence of increased systemic venous pressure, with prominent pulsations of the cervical veins. Cardiac catheterization gave almost the same results as previously, except that there was some question of mitral insufficiency associated with an atrial septal defect.

On November 13, 1956, thoracotomy revealed an enlarged right ventricle and right atrium. Unexpectedly, constrictive pericarditis with calcification of the pericardium overlying the right atrium was encountered. Although the pericardium was adherent throughout, the major portion of adherence was over the right atrium. Pericardial resection was successfully done, and then, with the aid of temporary extracorporeal circulation, an ordinary atrial septal defect of moderate size was repaired. Although the tricuspid valve appeared to be normal, it was definitely insufficient. No mitral insufficiency was detected.

The patient's postoperative course was prolonged, and was complicated by an extremely difficult bronchopulmonary suppurative process. Copious purulent secre-

tions were aspirated, and respiratory difficulties increased, necessitating tracheotomy. In addition, nonunion of the sternum developed. Recovery was slow, requiring increased amounts of antibiotics and supportive therapy. Nine months later, however, the patient appeared to be clinically improved.

*Case 4.* A 41 year old unmarried female clubroom attendant came to the Mayo Clinic for cardiac evaluation on July 7, 1959. A heart murmur had been noted when she was four years old. Peripheral cyanosis had been observed during youth, but there was no history of orthopnea or squatting.

Except for episodic palpitation, the patient had had only slight difficulty until December, 1958, when she had a sore throat associated with an upper respiratory infection. Since then she had been aware of progressive fatigue, dyspnea and peripheral edema, accompanied by lassitude and asthenia. Some improvement followed the taking of digitalis and hydrochlorothiazide six days a week. She had had thoracic-wall, muscular-type pains intermittently during the preceding four months.

There was no history of rheumatic fever, pulmonary embolism or previous surgery.

On examination, the blood pressure was 120/90 mm. of Hg. The patient had mild cyanosis, and clubbing of the fingers and toes. Evidence of increased venous pressure included marked distention of the jugular veins, and a systolic dip was present. Moderate ascites was accompanied by peripheral edema of the ankles. The heart was quiet, and a grade 2, coarse, ejection type of systolic murmur was heard best in the left second and third intercostal spaces. In the left third interspace the second sound was decreased, being followed by a transient and variable third sound considered to be of atrial origin. The edge of the liver was palpated 3 cm. below the costal margin and was slightly tender. No "paradoxical" pulse was demonstrable.

An electrocardiogram revealed atrial fibrillation, with a ventricular rate of 52 per minute. QRS complexes were of low amplitude (figure 1c). Right axis deviation plus right ventricular configuration in the precordial leads was consistent with right ventricular hypertrophy. X-ray examination showed gigantic enlargement (globular type) of the cardiac silhouette (figure 2d). The supracardiac vascular pedicle was narrow, and the pulmonary vasculature was slightly decreased. Fluoroscopy disclosed marked cardiac enlargement, involving all chambers. Cardiovascular pulsations were abnormally decreased. No intracardiac calcification was seen. Hospitalization and anticongestive measures for heart failure, including the use of digitoxin, diuretics, salt restriction and rest in bed, produced slight improvement.

Laboratory data were: concentration of hemoglobin and the leukocyte, erythrocyte and differential blood counts, normal; specific gravity of the urine, 1.024; albuminuria, grade 1; erythrocyturia, grade 1; serologic reaction for syphilis, negative; serum potassium, 3.3 mEq.; tests for lupus erythematosus cells, negative; urinary 5-hydroxyindoleacetic acid, absent; blood urea, 55 mg.; sulfobromophthalein retention, grade 2 (20%) in 1 hour; serum electrophoretic values: 7.01 gm. for total protein, 2.78 gm. for albumin, 0.35 gm. for alpha-1-globulin, 0.41 gm. for alpha-2-globulin, 1.85 gm. for beta-globulin, and 2.62 gm. (almost twice normal) for gamma-globulin; serum cholesterol, 144 mg.; serum bilirubin, negative by the direct reaction and 1.5 mg. by the indirect reaction.

Cardiac catheterization revealed severe pulmonic stenosis, with a systolic gradient of approximately 200 mm. of mercury across the pulmonic valve (table 2). A roentgenogram showed the catheter to be looped in the right atrium, and a considerable proportion of the apparent cardiac enlargement to be due to pericardial effusion (figure 3). Congestive heart failure was present, and the cardiac output was low. No evidence of an abnormal intracardiac communication was obtained from oxygen-saturation data and dye-dilution curves.



A subxiphoid pericardiocentesis was performed on July 16, 1959, and 1,200 c.c. of amber fluid were removed. The initial intrapericardiac pressure was 0 on inspiration and plus 2 cm. of water on expiration. The pericardial fluid contained 2,400 leukocytes per cubic millimeter, representing 9% polymorphonuclear cells, 2% lymphocytes, and 89% cells that were unidentifiable. Cytologic study of the pericardial fluid for malignant cells gave negative results. Cultures for pyogenic organisms, acid-fast bacilli and fungi were sterile. Protein in the pericardial fluid measured 4.45 gm. per 100 c.c.

At thoracotomy on July 23, 1959, approximately 1,200 c.c. of serous pericardial fluid were evacuated. The pericardium was slightly thickened but did not appear

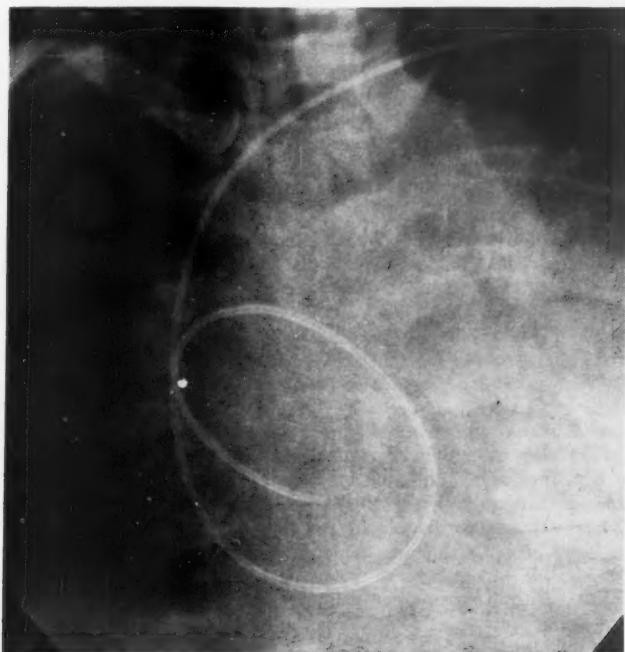


FIG. 3. Case 4. View showing that catheter is looped in right atrium, and that apparent cardiac enlargement is due to pericardial effusion.

to manifest any intrinsic disease. The right ventricle was markedly hypertrophied, and the right atrium was dilated and quite immobile. Some organized thrombus material was found in the right atrial appendage. The main pulmonary artery showed moderate poststenotic dilatation. Palpation of the atrial septum revealed no defects. There was a grade 1 to 2 tricuspid insufficiency before repair. Opening of the right ventricle disclosed a tightly stenotic pulmonary valve, having a lumen of about 5 mm.; only two vestigial commissures were identified. The outflow tract was markedly hypertrophied, and constricted tightly about the finger during systole. The ventricular septum was intact.

Extracorporeal circulation was begun and the pulmonary valve was opened

wide. A large amount of hypertrophied infundibular muscle was excised right up to the valve ring, with relief of the stenosis. A small opening was made temporarily through the diaphragm, and about 1,500 c.c. of peritoneal fluid were evacuated. A large "window" was made between the pericardial space and the right pleural space, and a catheter led out from each of these spaces. At operation, right ventricular pressure was 220/14 mm. of Hg, and systemic venous pressure, 14 (mean). Immediately after operation the pressures were 57/10 mm. of Hg in the right ventricle and 28/12 mm. of Hg in the right atrium.

The postoperative course was complicated by persistent increase of venous pressure, associated with mild congestive failure. The patient returned to her home community. Approximately three months later she died suddenly while hospitalized for treatment of her congestive failure. Necropsy was not performed.

*Case 5.* A 47 year old unmarried female instructor in physical education was referred on July 22, 1959, for cardiac evaluation prior to contemplated repair of a symptomatic right femoral hernia. Birth, infancy and early childhood had been normal. Scarlet fever at the age of five years had caused no apparent complications. A cardiac murmur was discovered at the age of 12 years during a physical examination at high school. In 1940, when the patient was 28 years old, a physician who saw her because of thoracic pain that followed a streptococcal sore throat told her that her heart was "enlarged." Thereafter she noticed gradual development of chronic fatigue and mild orthostatic edema of the ankles.

There was no history of exertional dyspnea, hemoptysis, rheumatic fever or tuberculosis. Raynaud's phenomena had been observed for many years, having occurred also in the patient's brother. Subjective cyanosis of the fingers and lips on exertion had been present since 1937. For more than 10 years she had had recurrent anterior thoracic pains which were not definitely related to exertion and which would reappear while she was relaxing; they were regarded as muscular in origin. Since 1946 she had had occasional episodes of orthopnea, swelling of the ankles and palpitation lasting two or three days. In 1950, one hour after hysterectomy for uterine fibroids, signs of shock appeared but quickly subsided after blood transfusion.

The patient was able to walk six to seven blocks before becoming dyspneic. Her main complaint during the preceding year had been aching in the legs at night or after prolonged sitting or standing. She had taken digitalis since June, 1959.

On physical examination the blood pressure was 126/84 mm. of Hg. There was no evidence of cyanosis or clubbing. The heart was not overly active. The apical impulse was palpable in the seventh intercostal space in the left midclavicular line. The first sound was split, with accentuation of the second component, followed by a grade 1 systolic murmur, audible best over the left second and third interspaces, and also along the left sternal border to the apex. The second sound was normal, and no diastolic murmur was audible. A right femoral hernia was reducible.

An electrocardiogram showed a sinus rhythm at a rate of 62, and right axis deviation. Low amplitude of the QRS complexes was noted in the standard leads, and QR complexes in Lead V-1. The electrocardiographic findings were consistent with right ventricular hypertrophy associated with incomplete right bundle branch block.

A roentgenogram revealed a small aortic arch, slight increase of pulmonary vasculature, and marked cardiac enlargement (figure 2e). Fluoroscopy disclosed decreased cardiac pulsations; enlargement of individual chambers could not be determined. The possibility of pericardial effusion was suggested.

Routine laboratory data were normal.

Cardiac catheterization revealed the presence of a 75% left-to-right shunt at the atrial level (table 2). Pulmonary artery and right ventricular pressures were at the high range of normal, and right atrial pressure was slightly increased.

On July 29, approximately 200 c.c. of fluid were removed by subxiphoid pericardiocentesis; the fluid was clear but later was blood-tinged, and contained 2.35 gm. of protein per 100 c.c.

The patient returned on August 28, 1959, for repair of the atrial septal defect. At operation the pericardium was filled with bloody fluid, about a liter of which was removed. The atrial septal defect was small and was located posteriorly, in the midportion of the atrial septum. A patch of noncompressed polyvinyl (ivalon) sponge, 2 cm. in diameter, was sutured into the defect. A portion of excised pericardium showed histologically slight, nonspecific chronic inflammation, with moderate fibrosis. Culture of pericardial tissue was negative for pyogenic organisms. The patient had an uneventful postoperative course.

*Case 6.* A 48 year old, gravida 1, para 1 housewife was admitted to the hospital on March 22, 1954, because of progressive dyspnea and cardiac palpitation of five years' duration, associated with generalized fatigue during the preceding six months. A heart lesion had been recognized since the age of 15 years, when she had had scarlet fever. She had had an uncomplicated pregnancy at the age of 38. Chronic myocardial failure had been a problem since the age of 42 years. Digitoxin, a low salt diet and mercurial diuretics were required for relief of recurrent peripheral edema and ascites which contributed to her progressive exertional dyspnea. She was unable to do housework, and dyspnea became prominent after she climbed one flight of stairs. There was no history of orthopnea or episodic nocturnal dyspnea.

On examination, the patient's blood pressure was 120/90 mm. of Hg. She had grade 3 distention of the cervical veins. No digital clubbing or peripheral cyanosis was noted. A prolonged apical systolic murmur of grade 2 intensity was accompanied by a thrill over the left third intercostal space. A faint mid-diastolic rumble was audible at the apex when the patient was sitting upright. The second sound in the left second interspace was split and the pulmonary component was accentuated, grade 2. A basal systolic bruit was loudest in the left second interspace, and was also heard over the neck and in the right second interspace. The liver and spleen were enlarged, and there was grade 2 pedal edema to the level of the knees. Laboratory data were normal.

An electrocardiogram revealed right ventricular hypertrophy (figure 1d), associated with atrial flutter and varying atrioventricular block. A roentgenogram disclosed marked cardiomegaly, involving mostly the right ventricle (figure 2f). Also, the main pulmonary artery and the peripheral pulmonary vessels were much enlarged. Left atrial enlargement was noted during cardiac fluoroscopy. Cardiac catheterization revealed a 75% arteriovenous shunt at the atrial level, associated with marked pulmonary hypertension (table 2). The roentgenograms taken with the loop of catheter lying against the right atrial wall suggested the presence of a large pericardial effusion.

The patient responded fairly well to diuretic therapy, with a decrease of 10 pounds within five days; however, she still had marked cardiac disability and limited exercise tolerance.

Thoracotomy, performed on April 5, 1954, revealed between 1,000 and 1,500 c.c. of coffee-colored fluid in the pericardial space. A defect in the atrial septum, measuring approximately 6 by 4 cm., was found in the usual location, in conjunction with mild tricuspid insufficiency. Shortly after the atrial well was stitched in place, cardiac arrest occurred and proceeded quickly to ventricular fibrillation, which failed to respond to electrical defibrillation and to intracardiac administration of calcium gluconate and epinephrine. Necropsy confirmed the previously mentioned operative findings.

## OBSERVATIONS

Nearly all of the patients had symptoms of easy fatigability and dyspnea on exertion, associated with increased systemic venous pressure, yet orthopnea was conspicuously absent in five and equivocal in one. Precordial pain was another common complaint, described usually as a diffuse, thoracic-wall, muscular type of discomfort, and not necessarily related to effort.

All of the patients had a systolic murmur, varying in intensity from grade 1 to 2, and heard best either over the left second and third intercostal spaces or near the region of the cardiac apex. Diastolic murmurs were notably absent in all but case 6, in whom a faint mid-diastolic murmur was heard at the apex. The second sound in the left second and third intercostal spaces was considered to be accentuated in three patients, normal in two, and decreased in one. The last mentioned patient had pulmonic stenosis, and was also the only one manifesting mild cyanosis and slight clubbing of the fingers. A transient friction rub was audible in two, and a "paradoxical" pulse was elicited in one.

Generalized cardiac enlargement was uniformly seen on the thoracic roentgenograms, and the pulmonary vascular markings were increased in all but the patient with pulmonic stenosis, the latter having normal pulmonary vasculature. Decreased cardiovascular pulsations were observed during fluoroscopy in cases 2, 4 and 5. In the other three patients with normal cardiac pulsations, one wonders whether the hyperkinetic effects of excessive pulmonary blood flow consequent to the large left-to-right shunt tended to be counterbalanced by the presence of chronic pericardial compression.

All of the patients had electrocardiographic evidence of right ventricular hypertrophy and, in addition, two had right bundle branch block. Right axis deviation was uniformly present, with the mean QRS electrical axis ranging from plus  $110^{\circ}$  to plus  $125^{\circ}$ . A suggestive clue to the occurrence of pericardial compression was the finding of low amplitude of the QRS complexes in two patients (figures 1a and c), and borderline amplitude in a third.

At cardiac catheterization, pressure in the brachial veins and right atrium was abnormally increased in five patients and at the upper limit of normal in one. Two thirds of the patients had increased diastolic pressure in the right ventricle, and only case 1 had an early diastolic dip followed by an elevated diastolic plateau compatible with impaired diastolic filling of the ventricle. The catheter passed through an interatrial communication in three of the patients. Left atrial pressure was moderately increased, with a corresponding increase in pulmonary artery pressure, in four patients, and severe pulmonary hypertension occurred in one. All had normal arterial systolic, diastolic and pulse pressures.

The oxygen saturation of the systemic arterial blood was normal in all

except the patient with pulmonic stenosis, who had a radial artery saturation of 93%. A transatrial arteriovenous shunt of more than 45% was present in five patients, being absent only in the patient with pulmonic stenosis. From dye-dilution curves a venoarterial shunt of 5% was detected in case 1, and of 12% in case 3.

Thus, cardiac catheterization data identified the intracardiac defect in all six patients, and additional evidence suggested the coexistence of pericardial disease in cases 1, 4 and 6.

#### COMMENT

Despite the infrequent and probably chance occurrence of pericardial disease in patients having congenital heart lesions, it is important to distinguish such patients from those having the complication of congestive heart failure.

Right ventricular failure consequent to congenital septal defects is accompanied by increased venous and right atrial pressures, usually in conjunction with increased pulmonary vascular resistance. Reversal of the intracardiac shunt occurs, with considerable blood being shunted right to left, and leading to arterial oxygen desaturation and cyanosis. Differentiation from tricuspid insufficiency may also be difficult, yet it is possible, if one observes a systolic expansion of the jugular pulse, detects intensification of the systolic murmur during inspiration,<sup>10</sup> and palpates a pulsatile liver. In addition, tricuspid insufficiency may be demonstrated by dye-dilution technics at cardiac catheterization.<sup>11</sup>

The suspicion of the coexistence of pericardial compression with congenital heart disease warrants surgical consideration, and complete correction may be offered at an acceptable risk. The only operative death in the present group concerned case 6, who had marked pulmonary hypertension and an atrial septal defect in addition to a large pericardial effusion. Ventricular fibrillation and cardiac arrest occurred suddenly during operation, and failed to respond to defibrillatory measures. The other five patients underwent thoracotomy, with successful alleviation of their pericardial disease and repair of their intracardiac defects. (Case 4 died about three months postoperatively, as noted.) Cases 4 and 5 had preoperative pericardiocentesis for their large pericardial effusions, while cases 1 and 2 had pericardial biopsy and decortication of their constrictive pericarditis prior to closure of their atrial septal defects. The "commissurotomy syndrome"<sup>12</sup> was not observed in any of these patients.

The pathogenesis of the pericardial disease in these patients still remains an enigma. In none was there a history of antecedent rheumatic fever, tuberculosis, or trauma to the thorax. The usual laboratory studies revealed no consistent abnormality. Histologic and cytologic examination of the pericardial tissue and fluid similarly failed to disclose the underlying cause. However, in case 2, acute pericarditis occurred prior to thoracotomy, and

probably contributed to the operative finding of coexistent fibrinous pericarditis and mild pericardial effusion.

No single pathognomonic clinical or laboratory finding was uniformly present in these patients. Hence, when confronted with a patient presenting the clinical manifestations of congestive heart failure in association with a congenital intracardiac defect, one should remember the possibility of coexistent pericardial disease, especially if there is a high venous pressure with little or no right-to-left shunt and with normal oxygen saturation of the arterial blood. This should prompt further search for the various though subtle manifestations of associated pericardial disease, such as a nonpalpable apex beat, friction rub, diastolic precordial thrust,<sup>13</sup> low amplitude of the QRS complexes in the electrocardiogram, pericardial calcification, and decreased cardiovascular pulsations observed during fluoroscopy.

#### SUMMARY

Pericardial disease superimposed upon a congenital cardiac lesion is uncommon, and probably has only a chance relationship. When it does occur, it results in problems of diagnosis and treatment not usually encountered.

Six patients who had this combination are reported. Four had an atrial septal defect; two of these also had constrictive pericarditis, and the other two had pericardial effusion. One had severe pulmonic stenosis plus a large pericardial effusion, and another had a partial anomalous pulmonary venous connection and fibrinous pericarditis. All patients underwent cardiac catheterization and surgical repair.

In a patient with a congenital heart lesion, it is important to distinguish complicating pericardial disease from congestive failure.

#### ACKNOWLEDGMENTS

We are indebted to Dr. E. H. Wood and his co-workers in the cardiovascular laboratory for performing the cardiac catheterizations on these patients. We also wish to thank Dr. H. B. Burchell, Dr. R. E. Smith, Dr. F. H. Ellis, Jr., and Dr. D. C. McGoon for their cooperation in this study.

#### SUMMARIO IN INTERLINGUA

Morbo pericardial superimponite a un congenite lesion del corde es pauco commun e occurre probabilemente per coincidentia solmente. Quando illo es presente, illo resulta in problemas diagnostic e therapeutic non usualmente incontrate. Le presente articulo reporta sex casos del mentionate combination. In quatro del patientes il habeva un defecto atrio-septal. Duo del quatro habeva etiam pericarditis constrictive, le altere duo effusion pericardial. Le quinte patiente habeva sever stenosis pulmonic insimul con marcate effusion pericardial, e le ultime habeva un anormal connexion partial pulmono-venose e pericarditis fibrinose. In omne le casos, catheterismo cardiac e reparo chirurgic esseva effectuate. In patientes con congenite lesion cardiac, il es importante distinguer le existentia complicatori de morbo pericardial ab disfallimento congestive.



## BIBLIOGRAPHY

1. Taussig, H. B.: Congenital malformations of the heart, 1947, The Commonwealth Fund, New York.
2. Plachta, A., and Speer, F. P.: Congenital absence of the right coronary artery: report of a case associated with adherent pericardium and augmented pericardial vascularity, *Am. J. Clin. Path.* **24**: 1035, 1954.
3. Summers, J. B., Stanley, A. L., and Stringer, C. J.: Unusual case report: coarctation of the aorta, constrictive pericarditis and pleuritis, and primary carcinoma of the liver occurring in one person, *J. Indiana M. A.* **47**: 1294, 1954.
4. White, P. D.: Chronic constrictive pericarditis, *Circulation* **4**: 288, 1951.
5. White, P. D.: Heart disease, 4th ed., 1951, The Macmillan Company, New York.
6. Wood, P.: Diseases of the heart and circulation, 2nd ed., 1956, J. B. Lippincott Company, Philadelphia.
7. Friedberg, C. K.: Diseases of the heart, 2nd ed., 1956, W. B. Saunders Company, Philadelphia.
8. Wood, E. H.: Special technics of value in the cardiac catheterization laboratory, *Proc. Staff Meet., Mayo Clin.* **28**: 58, 1953.
9. Barratt-Boyes, B. G., and Wood, E. H.: The oxygen saturation of blood in the venae cavae, right-heart chambers, and pulmonary vessels of healthy subjects, *J. Lab. and Clin. Med.* **50**: 93, 1957.
10. Carvallo, J. M. R.: Signo para el diagnostico de las insuficiencias tricuspideas, *Arch. Inst. cardiol. México* **16**: 531, 1946.
11. Bajec, D. F., Birkhead, N. C., Carter, S. A., and Wood, E. H.: Localization and estimation of severity of regurgitant flow at the pulmonary and tricuspid valves, *Proc. Staff. Meet., Mayo Clin.* **33**: 569, 1958.
12. Lisan, P., Reale, A., and Likoff, W.: The postmitral commissurotomy syndrome: a four-year clinical, pathologic and serologic study, and its relation to restenosis, *Ann. Int. Med.* **50**: 1352-1358 (June) 1959.
13. Durant, T. M.: The recognition of pericardial disease, *Mod. Concepts Cardiovas. Dis.* **27**: 455, 1958.

## THALASSEMIA IN "NON-MEDITERRANEAN" FAMILIES \*

By WILLIAM McFARLAND, Commander (MC) USN, and HOWARD A.  
PEARSON, Lieutenant (MC) USN, *Bethesda, Maryland*

IN 1925 and 1927 Cooley and Lee<sup>1,2</sup> described an anemia peculiar to individuals of Greek or Italian origin. Subsequently, the disease has been so thoroughly studied and documented that thalassemia is one of the first diagnostic considerations in an individual of "Mediterranean background" who presents with hypochromic anemia. However, the disease is rarely entertained as a diagnostic possibility in the absence of such an ethnic background, in spite of the fact that there have been numerous reports of the disease in other racial groups in almost all parts of the world.

TABLE 1

Tabulation of Clinical and Laboratory Data in Six Patients with Thalassemia Trait

Case	Racial Back-ground	Age	Sex	Jaundice	Liver	Spleen	Hgb. (gm.%)	Hct. (%)	Mean Corp. Vol. ( $\mu^3$ )	Mean Corp. Hgb. (γγ)	Mean Corp. Hgb. Conc. (%)	Retics. (%)	Bili-rubin (mg.%)
1	English	62	F	+	↓8 cm.	↓4 cm.	8.0	33	76	21	24	10.6	3.6
2	Danish	55	M	0	—	—	10.6	34	70	22	31	3.0	0.5
3	English	29	M	0	—	—	13.0	38	70	24	34	0.7	1.0
4	Negro	47	M	0	—	—	9.6	33	72	22	29	3.6	0.6
5	Filipino	59	M	0	—	—	10.2	34	71	21	30	3.0	0.8
6	Scottish	36	F	0	—	—	10.5	35	77	23	30	1.4	0.8
(Normal values)													

Case	Osmotic Fragility	Serum Iron ( $\mu\text{g.}\%$ )	Fetal Hgb. (%)	Hgb. A <sub>2</sub> (% of Hgb.)	Bone Marrow M:E Ratio	RBC Survival (days T <sub>1/2</sub> —Cr <sup>51</sup> )	Plasma Fe <sup>59</sup> Disappearance (min. T <sub>1/2</sub> )	Plasma Fe <sup>59</sup> Turnover (mg./kg./day)	RBC Fe <sup>59</sup> Utilization (% in 10 days)
1	Decr.	153	2.6	4.6	0.5/1	15	17	1.94	42
2	Decr.	180	4.6	6.3	0.5/1	19	30	2.80	58
3	Decr.	120	0.6	4.6	1.5/1	20.8	78	1.00	62
4	Decr.	100	2.2	5.9	0.8/1	21	50	1.40	58
5	Decr.	150	4.0	5.2	0.6/1	25.5	80	0.84	62
6	Decr.	230	1.5	4.5	1.1/1	27	98	1.00	63
(Normal values)									
		80–150	<2.0	<3.2	2/1	25–35	60–120	0.4–0.6	>80

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From the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

Requests for reprints should be addressed to William McFarland, M.D., U. S. Naval Hospital, Bethesda 14, Maryland.

One reason for hesitancy to diagnose thalassemia in the absence of a "Mediterranean background" may be that, until recent years, the diagnosis was based on relatively nonspecific criteria, such as abnormal red cell morphology. At present, however, with the availability of more specific diagnostic methods, the diagnosis can be made more readily and with greater finality, and it will probably be made more frequently. This statement is based on the fact that in the last two years we have diagnosed thalassemia trait in six individuals of various "non-Mediterranean backgrounds," including Danish, English, Scottish, Filipino and Negro. It is the purpose of this report to present clinical and laboratory data on this group of patients to reemphasize the probability that mild forms of the disease are more common and more widespread than generally recognized.

#### CASE REPORTS

*Case 1.\** A 62 year old female of English descent with a lifelong history of anemia, treated with various medications, had received about 30 blood transfusions within the eight-year period prior to admission.

Her mother was said to have died of pernicious anemia. Her only brother and his only daughter had anemia, with red cell morphologic changes similar to the patient's. Both the brother and his daughter had been thoroughly studied elsewhere, and finally underwent splenectomy in an effort to improve their anemias.

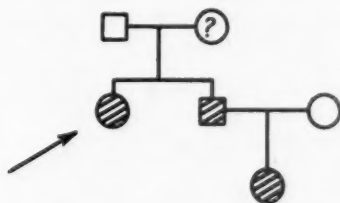


FIG. 1. Pedigree of case 1.

On physical examination, the patient had scleral icterus and mottled brown pigmentation over the lower extremities. The liver extended 8 cm. and the spleen 4 cm. below the costal margins.

Pertinent laboratory data are recorded in table 1. There were no abnormal bone structures on x-ray examination. Liver function tests were essentially normal; however, needle biopsy of the liver showed marked hemosiderosis.

Figure 1 is a diagram of affected members of the family (the arrow indicates the proband in each case.)

*Case 2.* This 55 year old retired naval captain of Danish ancestry claimed that his genealogy had been traced to William the Conqueror! Except for his maternal grandmother, who was Alsatian, his family consisted entirely of Danes. The patient was asymptomatic, but had become aware of mild anemia as a result of routine annual physical examinations. Physical examination was within normal limits. Pertinent

\*We are indebted to Dr. W. Dameshek for the opportunity of reporting this patient, to Dr. M. Baldini for ferrokinetic studies, and to Dr. P. S. Gerald for hemoglobin A<sub>2</sub> determination.

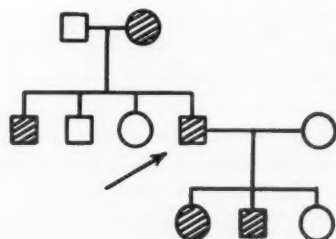


FIG. 2. Pedigree of case 3.

laboratory results are listed in table 1. The patient's daughter, the only family member available for study, did not have thalassemia trait.

*Case 3.\** Anemia had been discovered in a 29 year old male of English-French extraction during the course of a hospital admission for abdominal pain. The patient stated that he had been rejected as a blood donor in 1957 because of anemia. One brother had been anemic for several years. Physical examination was essentially negative. Pertinent laboratory results are recorded in table 1. Affected members of the family are shown in figure 2.

*Case 4.* A 47 year old Negro male was admitted to the hospital with symptoms of cough, chest pain and fever. A lung abscess was discovered and treated. Persistent anemia proved to be due to thalassemia trait. There was no family history of anemia, and no other members of the family were available for study.

*Case 5.* A 59 year old Filipino male was referred to the hospital for a Schilling test. The patient had complained of generalized weakness, and a blood count revealed mild anemia. There was no family history of anemia, and no other members of the family were available for study.

*Case 6.* A 36 year old female of Scottish extraction was referred to the hospital for a Schilling test. Mild anemia had been discovered on a routine blood count, and the patient's mother was supposed to have had pernicious anemia. Family studies failed to reveal the disease in other members of her family, as shown in figure 3.

#### METHODS

Routine blood studies were performed, using standard hematologic techniques. Osmotic fragility tests were done by the method of Dacie.<sup>3</sup> Serum iron levels were measured by a modification of the method of Moss and

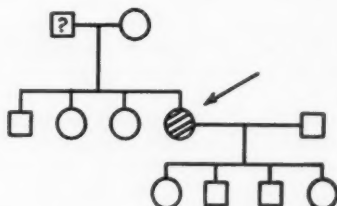


FIG. 3. Pedigree of case 6.

\* We are indebted to Dr. J. Brook for the opportunity of studying this patient and his family.

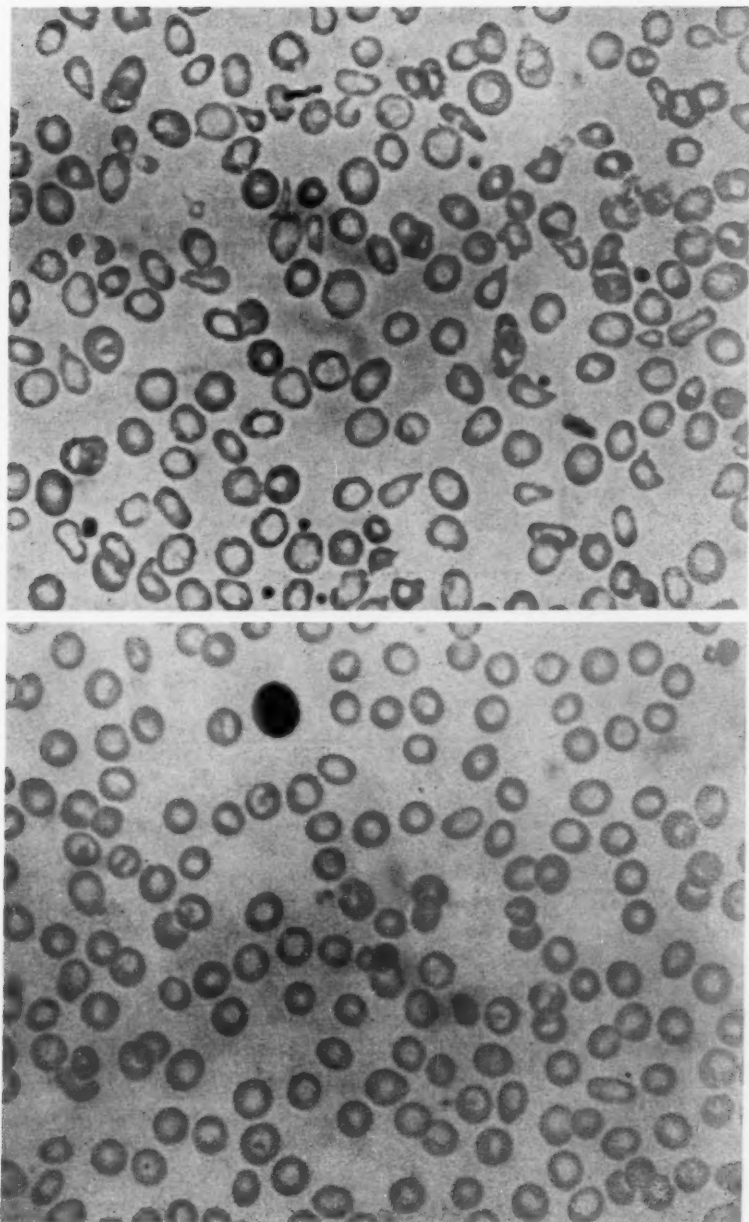


FIG. 4. Representative photomicrographs ( $\times 270$ ) of stained blood films, demonstrating the two extremes of red cell morphologic changes encountered in this group of patients. *A* (above): Blood film of case 1. *B* (below): Blood film of case 3.

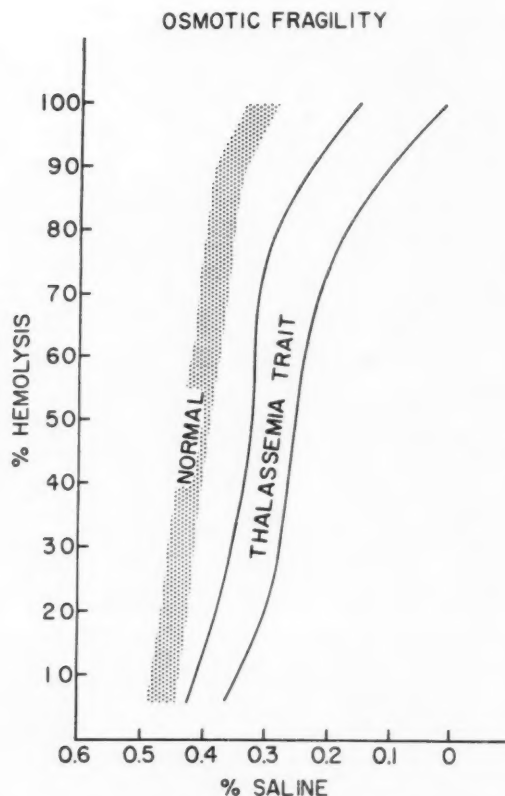


FIG. 5. Composite drawing of the osmotic fragility curves.

Mellon.<sup>4</sup> The myeloid erythroid ratio of the bone marrow was based on 1,000 cell counts. Fetal hemoglobin was measured by the one-minute method of Singer et al.<sup>5</sup> Starch block electrophoresis of hemoglobin was performed using barbital buffer of pH 8.6, as previously described.<sup>6</sup> Studies of red cell survival, using  $\text{Cr}^{51}$ , and ferrokinetic measurements, using  $\text{Fe}^{59}$ , were carried out in a combined procedure, employing gamma ray spectrometry.<sup>7</sup> The tracer dose of  $\text{Fe}^{59}$  was incubated with normal donor plasma prior to administration to obviate discrepancies arising from abnormalities of the patient's iron-binding capacity.

#### RESULTS

There were abnormalities of red cell morphology in each case, as demonstrated in figure 4. Results of the various laboratory tests are shown in table 1.



Case 1 was the only patient of this group who had abnormal physical findings related to anemia. This suggests that her case represented an intermediate form of the disease. In contrast, the other patients fit into the so-called thalassemia minor group. Case 1 also had the lowest hemoglobin level (8.0 gm.%), 10.6% reticulocytes, and a total bilirubin of 3.6 mg.%. None of the other patients had bilirubinemia, although several had slight elevations of reticulocyte counts. The mean corpuscular volume was low in each case, and each showed a decrease in osmotic fragility (figure 5). Serum iron levels were normal in four patients and elevated in two. Fetal

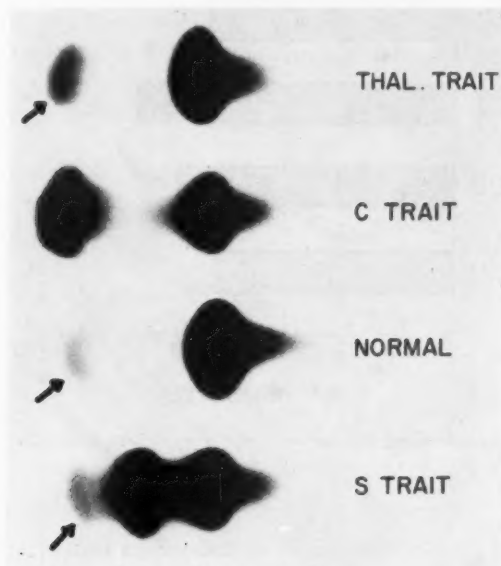


FIG. 6. Photograph of a typical starch block. Cyanmethemoglobin has been applied to the left and has migrated toward the right. The arrows indicate hemoglobin A<sub>2</sub>. In the case of C trait, the large amount of hemoglobin C obscures the hemoglobin A<sub>2</sub>.

hemoglobin levels were elevated in four patients; hemoglobin A<sub>2</sub> was abnormally high in all patients (figure 7). Bone marrow aspirations showed erythroid hyperplasia in each instance.

Red cell survival, as measured by Cr<sup>51</sup> T<sub>1</sub>, was abnormally short in four patients, but within normal limits in the other two, as demonstrated in figure 8A. Plasma iron disappearance was abnormally rapid in three patients (figure 8B), whereas calculation of plasma iron turnover gave abnormal results in all patients. The low values for iron utilization by red cells (figure 8C) were also consistent.

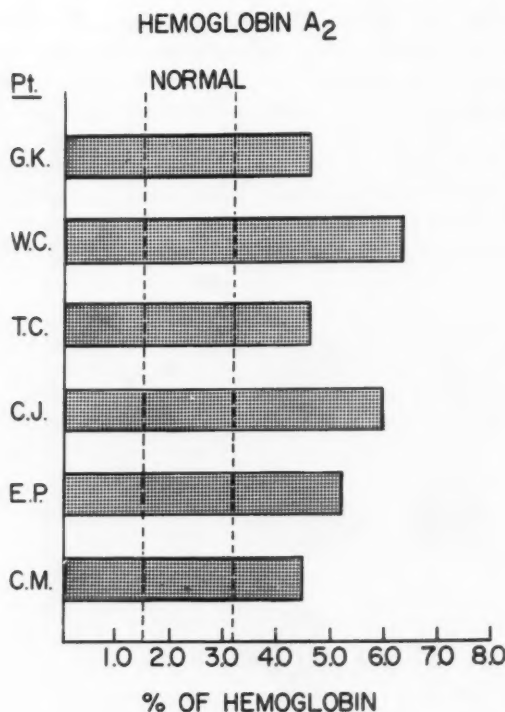


FIG. 7. Graph demonstrating the degree of elevation of hemoglobin A<sub>2</sub> in each patient.

#### DISCUSSION

Until recent years, the diagnosis of thalassemia trait was based on findings of hypochromia, microcytosis, target cells, decreased red cell fragility, refractoriness to iron therapy, and positive family studies.<sup>8</sup> To this list can be added the demonstration of normal or high serum<sup>9</sup> and bone marrow iron, elevated fetal hemoglobin,<sup>5</sup> elevated hemoglobin A<sub>2</sub><sup>10</sup> and radioisotope studies indicating defective iron metabolism.<sup>11, 12</sup> Our patients demonstrated these changes in various degrees, usually consistent with the severity of the clinical picture. The studies that were most valuable—that is, that were invariably abnormal regardless of the clinical picture—were mean corpuscular volume, osmotic fragility, hemoglobin A<sub>2</sub>, bone marrow M:E ratio, plasma iron turnover and iron utilization.

Since the red blood cell morphology on the stained blood film often provides the first clue to the diagnosis of thalassemia trait, the frequency of diagnosis depends to a great extent on the capabilities and alertness of the laboratory technicians doing routine blood counts. In general, the degree

of morphologic abnormality parallels the degree of clinical severity, as demonstrated in figure 4.

Of the newer diagnostic criteria, elevation of hemoglobin A<sub>2</sub> is one of the most consistent findings. This is a minor hemoglobin fraction which requires electrophoresis on starch block at pH 8.6 for its demonstration (figure 6).<sup>13</sup> Hemoglobin A<sub>2</sub> normally comprises less than 3.2% of total hemoglobin; values in our patients were consistently above this level (figure 7). Family studies showed remarkably constant levels of hemoglobin A<sub>2</sub> among affected members of any one family, as has been pointed out by Gerald and Diamond.<sup>10</sup> Instances of thalassemia with normal levels of hemoglobin A<sub>2</sub> are rare in Caucasians and were, until recently, unexplainable. However, recent investigations have shown that the globin moiety of hemoglobin A consists of two sets of polypeptide chains, designated  $\alpha_2$  and  $\beta_2$ .<sup>14, 15, 16</sup>

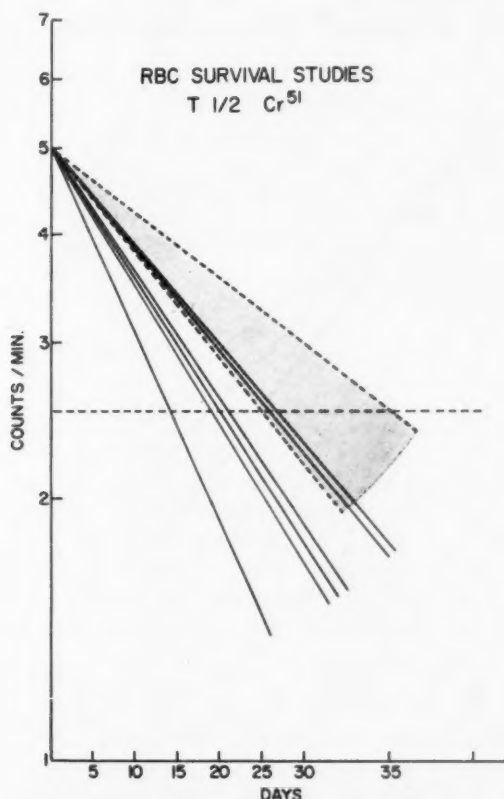


FIG. 8. A. Schematic representations of erythrokinetic data. (The shaded areas show ranges of normal for our laboratory.)

Genes for these two chains are nonallelic for each other, but the gene for  $\beta$  is allelic with those responsible for abnormal hemoglobins S, C and E. Ingram and Stretton<sup>17</sup> postulated that thalassemia results from mutations of genes controlling synthesis of either the  $\alpha$  or  $\beta$  chain. The  $\beta$  chain type is more common, and is associated with abnormally high hemoglobin A<sub>2</sub> levels, whereas the  $\alpha$  type is rare in Caucasians, and is characterized by normal hemoglobin A<sub>2</sub> levels.

The plasma Fe<sup>59</sup> turnover and the red cell Fe<sup>59</sup> utilization test were the most consistent of the erythrokinetic studies in demonstrating the defective iron metabolism characteristic of thalassemia. Our patients were all heterozygous for the disease and, as one might expect, the curves of iron utilization

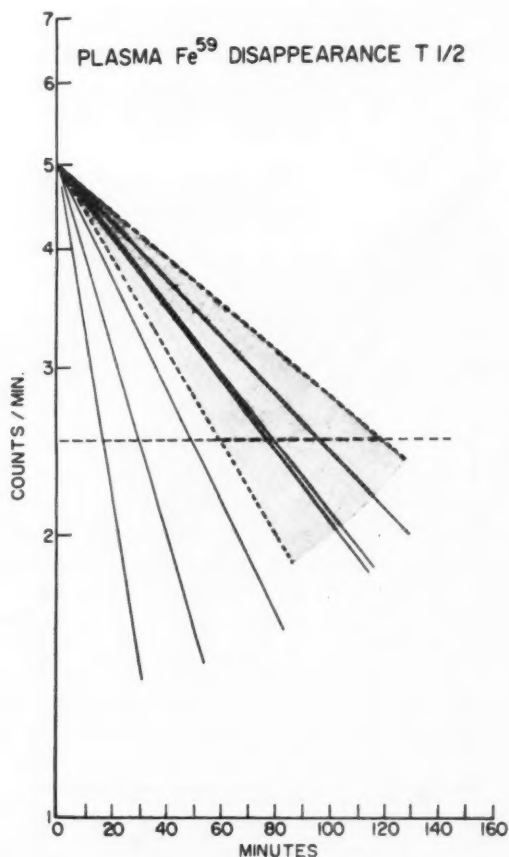
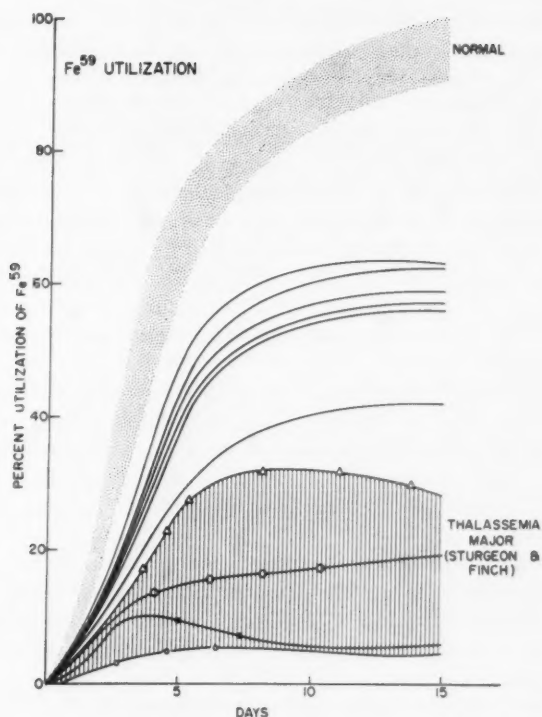


FIG. 8. B. Plasma Fe<sup>59</sup> disappearance half time.

FIG. 8. C. Per cent  $\text{Fe}^{59}$  utilization.

fell between normals and the curves of homozygous thalassemia, as studied by Sturgeon and Finch<sup>12</sup> (figure 8C).

The fact that the individual with thalassemia trait cannot utilize iron properly constitutes the main reason for establishing the diagnosis. Since the red cells appear to be hypochromic, these patients usually receive numerous courses of iron therapy, in an effort to improve their anemia. Generally, however, their iron stores are already overloaded as a result of years of increased iron absorption from the gastrointestinal tract. Needle biopsy of the liver in our first patient showed marked hemosiderosis, and although this procedure was not performed on any of the other patients, they all showed greatly increased bone marrow iron. One may reasonably assume that, if these patients do not already have hemosiderosis, they are likely to develop it, particularly if the tendency for increased iron storage is enhanced by courses of iron therapy. This point seems especially pertinent with the availability in recent years of very potent, parenteral iron products.

Should we continue to emphasize the racial aspects of thalassemia?

Apparently this problem concerned Dr. Cooley in 1941,<sup>18</sup> when he discussed the question of "race limited" disease in regard to thalassemia and sickle cell anemia. He stated: "My own opinion is that there is no such thing [as a race-limited disease]. When a disease-producing mutation takes place, it is evident that it will recur first in the neighborhood of its origin. . . . It will be limited to a community, a province or a race in proportion to the clannishness and the isolation of the people involved." He obviously objected to the acceptance of thalassemia as a racial disease, and preferred to consider it a spontaneous genetic mutation, just as we are forced to consider hemophilia in many instances. This still would not explain the high incidence of the gene in the Mediterranean area—unless, perhaps, as suggested for sickle cell trait,<sup>19</sup> heterozygosity for a hemoglobinopathy may afford a selective advantage.

Excellent studies of thalassemia in population groups (such as the people of Thailand,<sup>20</sup> the Sikhs in Vancouver, British Columbia,<sup>21</sup> and the Kurdistan Jews<sup>22</sup>) have pointed out the probable relation to early migrations of people from the Mediterranean basin. Certainly the broad expanse of the Roman Empire could account for instances of the gene in English, French and Spanish families.

In the ethnic "melting pot" of modern America, the precise delineation of racial backgrounds is obviously hazardous. Many third- or fourth-generation Americans have little knowledge of their racial ancestry, so that the racial aspects of a disease become relatively unimportant in considering a particular patient.

Efforts to minify the racial aspects of thalassemia might be more successful if the disease could be given a name devoid of racial connotations. In 1950 the Committee on Hematologic Nomenclature recommended that it be called "hereditary leptocytosis."<sup>23</sup> There are objections to this term, on the basis that leptocytes are found in other hemoglobinopathies.<sup>24</sup> However, broader use of it, or perhaps a better term, may increase the frequency of diagnosis, since the disease would become part of the differential diagnosis in most cases of chronic, hypochromic anemia, regardless of the patient's racial background.

#### SUMMARY

Clinical and laboratory data on six patients with heterozygous thalassemia have been presented to reemphasize the fact that a "Mediterranean background" is not essential for the diagnosis. Racial backgrounds in our patients included Danish, English, Scottish, Filipino and Negro. Newer diagnostic criteria have been discussed, with special emphasis on the demonstration of abnormal elevation of hemoglobin A<sub>2</sub> by starch block electrophoresis, and of defective iron metabolism by ferrokinetic studies. Wider use of these methods may increase the recognized incidence of the disease.



## SUMMARIO IN INTERLINGUA

Le diagnose de thalassemia se suggere prestemente in un subjecto anemic de provenientia grec o italian sed non in le absentia de un tal affiliation racial. Tamen, nos ha le impression que formas minor e intermediari de thalassemia es multo plus commun in familias non-mediterranee que lo que esseva recognoscite in le passato. Iste impression se basa super le facto que in le curso del passate anno nos ha diagnosticate thalassemia—in le routine de nostre travalo in un hospital general—in sex patientes de varie generes de origine "non-mediterranee," i.e. anglese, danese, scotic, philippin, e negre. Esseva presente, in omne le casos, le constataciones classic de anemia microcytic hypochromic, erythrocytos in forma de capello mexican, reduceite fragilitate erythrocytic, alte concentrationes de ferro seral, e hyperplasia erythroide del medulla ossee. Omne le patientes esseva studiate con respecto al superviventia del erythrocytos e al ferrocinetica, e omnes exhibiva anormalitates in congruentia con le severitate del imagine clinic. Hemoglobina A<sub>2</sub>, determinate per electrophorese a bloco de amylo, esseva augmentate sin exception. Studios familial esseva possibile in le majoritate del casos e supportava le diagnose de thalassemia heterozygotic. Nostre constataciones indica nettemente que thalassemia deberea esser prendite in consideration in omne patiente con anemia hypochromic, sin reguardo al affiliation racial, proque tal casos—si illos escappa al detection—pote haber serie consequentias per supercargation de ferro.

## BIBLIOGRAPHY

1. Cooley, T. B., and Lee, P.: A series of cases of splenomegaly in children, with anemia and peculiar bone changes, *Tr. Am. Pediat. Soc.* **37**: 29, 1925.
2. Cooley, T. B., Witwer, E. R., and Lee, P.: Anemia in children with splenomegaly and peculiar changes in bones: report of cases, *Am. J. Dis. Child.* **34**: 347, 1927.
3. Dacie, J. V.: *The haemolytic anemias*, 1954, Grune and Stratton, New York, p. 536.
4. Moss, M. L., and Mellon, M. G.: Colorimetric determinations of iron with 2, 2' bipyridyl and with 2, 2' 2<sup>13</sup> terpyridyl, *Indust. and Eng. Chem., Anal. Ed.* **14**: 862, 1942.
5. Singer, K., Chernoff, A. I., and Singer, L.: Studies on abnormal hemoglobins. I. Their demonstration in sickle cell anemia and other hematologic disorders by means of alkali denaturation, *Blood* **6**: 413, 1951.
6. Pearson, H. A., and McFarland, W.: Starch block electrophoresis of hemoglobin, *U. S. Armed Forces M. J.* **10**: 693, 1959.
7. Mitchell, T. G., Spencer, R. P., and King, E. R.: The use of radioisotopes in diagnostic hematologic procedures. III. Simultaneous Cr<sup>51</sup> and Fe<sup>59</sup> studies, *Am. J. Clin. Path.* **28**: 461, 1957.
8. Neel, J. V.: The detection of the genetic carriers of hereditary disease, *Am. J. Human Genet.* **1**: 19, 1949.
9. Smith, C. H., Sisson, T. R. C., Floyd, W. H., and Siegel, S.: Serum iron and iron-binding capacity of the serum in children with severe Mediterranean (Cooley's) anemia, *Pediatrics* **5**: 799, 1950.
10. Gerald, P. S., and Diamond, L. K.: The diagnosis of thalassemia trait by starch block electrophoresis of the hemoglobin, *Blood* **13**: 61, 1958.
11. Pearson, H. A., and McFarland, W.: Erythrokinetics in thalassemia trait, *J. Lab. and Clin. Med.*, in press.
12. Sturgeon, P., and Finch, C. A.: Erythrokinetics in Cooley's anemia, *Blood* **12**: 64, 1957.
13. Kunkel, H. G., and Wallenius, G.: New hemoglobin in normal adult blood, *Science* **122**: 288, 1955.
14. Rhinesmith, H. S., Schroeder, W. A., and Pauling, L.: A quantitative study of the hydrolysis of human dinitrophenyl (DNP) globin: the number and kind of polypeptide chains in normal adult human hemoglobin, *J. Am. Chem. Soc.* **79**: 4682, 1957.

15. Itano, H. A., and Singer, S. J.: On dissociation and recombination of human adult hemoglobins A, S and C, *Proc. Nat. Acad. Sc.* **44**: 522, 1958.
16. Itano, H. A., and Robinson, E.: Properties and inheritance of haemoglobin by asymmetric recombination, *Nature, London* **184**: 1468, 1959.
17. Ingram, V. M., and Stretton, A. O. W.: Genetic basis of the thalassaemia diseases, *Nature, London* **184**: 1903, 1959.
18. Cooley, T. B.: Hereditary factors in the blood dyscrasias (President's address), *Am. J. Dis. Child.* **62**: 1, 1941.
19. Allison, A. C.: Protection afforded by sickle-cell trait against subtertian malarial infection, *Brit. M. J.* **1**: 290, 1954.
20. Minnich, V., Na-Nakorn, S., Chongchareonsuk, S., and Kochaseni, S.: Mediterranean anemia. A study of thirty-two cases in Thailand, *Blood* **9**: 1, 1954.
21. Siddoo, J. K., Siddoo, S. K., Chase, W. H., Morgan-Dean, L., and Perry, W. H.: Thalassemia in Sikhs, *Blood* **11**: 197, 1956.
22. Matoth, Y., Shamir, Z., and Freundlich, E.: Thalassemia in Jews from Kurdistan, *Blood* **10**: 176, 1955.
23. Third, fourth and fifth reports of the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs, *Am. J. Clin. Path.* **20**: 562, 1950.
24. Dameshek, W.: "Thalassemia," or what's in a name, Editorial, *Blood* **10**: 293, 1955.

## HERPES ZOSTER IN HEMATOLOGIC NEOPLASIAS: SOME UNUSUAL MANIFESTATIONS \*

By EDWARD SHANBROM, M.D., SHERWOOD MILLER, M.D., and  
HELMUT HAAR, M.D., *Duarte, California*

WHILE it is generally known that herpes zoster commonly appears in malignant diseases, the frequency with which it occurs in lymphomas and leukemias has received surprisingly little comment in American literature in recent years. An excellent review of the subject by Craver and Haagen- sen appeared in 1932.<sup>1</sup> They reported on seven patients observed at Memorial Hospital, and discussed some of the concepts of the pathogenesis of the disorder. A more extensive report of herpes zoster occurring in 42 cases of leukemia reveals that this neurologic complication develops much more commonly in lymphocytic leukemia than in the granulocytic form.<sup>2</sup> Of 916 patients with herpes zoster seen at the Mayo Clinic, lymphoma was the most frequently associated diagnosis (39 cases, or 4.2%).<sup>3</sup> In a review of 5,778 patients with lymphomas and leukemias seen at Memorial Center, herpes zoster is reported as having occurred in 162 patients (2.8%).<sup>4</sup>

The development of herpes zoster in patients with lymphomas and leukemias often presents perplexing problems, both diagnostically and therapeutically. Awareness of the frequency with which this viral infection occurs in these diseases may prevent unnecessary diagnostic studies and "blind" therapeutic procedures which may be instituted in an attempt to relieve pain. It is the purpose of this paper to describe some of the clinical manifestations and certain unusual variations of herpes zoster that were observed in our patients.

### MATERIAL

The medical records of 475 patients with various blood dyscrasias were carefully reviewed. The majority of the patients had been under the medical supervision of the authors for a period of two years. With the exception of three cases, the clinical course of the herpes zoster in each patient was observed by us. There were 81 cases of acute leukemia included in this group, none of whom developed herpes. Of 303 patients with chronic leukemia, lymphoma or myeloma, herpes zoster developed during the course of their disease in 24, an incidence of 7.9%. Some clinical data on these patients are summarized in table 1.

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From the City of Hope Medical Center, Duarte, California, and Orange County General Hospital, Orange, California.

Requests for reprints should be addressed to Edward Shanbrom, M.D., Orange County General Hospital, Orange, California.

TABLE 1  
Clinical Data

Patient	Age	Sex	Diagnosis	CNS Segment Involved	Therapy at Onset of Herpes Zoster
1. WT	22	M	Hodgkin's disease	Cervical	Radiotherapy and uracil-mustard
2. RH	19	M	Hodgkin's disease	Generalized	Chlorambucil and "massive" prednisolone
3. ES	51	M	Hodgkin's disease	Cervical	Radiotherapy
4. RB	43	F	Hodgkin's disease	Thoracic	Radiotherapy
5. HW	19	F	Hodgkin's disease	Thoracic	Radiotherapy and chlorambucil
6. LR	28	F	Hodgkin's disease	Cervical	Chlorambucil
7. RM	49	F	Hodgkin's disease	Thoracic	Prednisolone and TEM
8. JR	49	M	Hodgkin's disease	Thoracic	Radiotherapy*
9. IM	34	M	Hodgkin's disease	Thoracic	Prednisolone
10. JP	17	F	Hodgkin's disease	Thoracic	Chlorambucil
11. SM	46	F	Lymphosarcoma	Cranial (VII)	Chlorambucil
12. RY	77	F	Lymphosarcoma	Cervical	Chlorambucil
13. EW	43	F	Lymphosarcoma	Lumbar	Prednisolone
14. EL	54	M	Lymphosarcoma	Lumbar	Prednisolone
15. HL	53	M	Chronic lymph. leukemia	Thoracic	Prednisolone
16. WL	44	M	Chronic lymph. leukemia	Lumbar	Prednisolone
17. ER	72	F	Chronic lymph. leukemia	Thoracic	Prednisolone
18. PJ	64	M	Chronic lymph. leukemia	Lumbar	Prednisolone
19. PH	45	M	Chronic lymph. leukemia	Thoracic	None
20. GM	49	M	Myeloma	Cranial (V)	Prednisolone
21. MM	64	F	Myeloma	Thoracic	Radioactive iodinated albumin
22. BW	54	F	Myeloma	Thoracic	None
23. LS	31	M	Chronic gran. leukemia	Thoracic	None
24. VB	54	F	Chronic gran. leukemia	Cervical	None

#### COMMENTS

As can be readily seen in table 1, herpes zoster occurred most frequently in patients with Hodgkin's disease. This is in keeping with observations of others.<sup>4</sup> On the other hand, only two patients with chronic granulocytic leukemia developed herpes zoster, and in one of these (case 23), the diagnosis of leukemia had not yet been established. Although it is not the purpose of this paper to discuss in detail the manifestations of herpes zoster observed in our patients, there are some clinical findings which deserve further comment and emphasis.

*Pain:* This was the most consistent and at times confusing presenting symptom. The pain appeared several days to several weeks before the development of the skin lesion. Although the distribution of the pain usually followed the distribution of the nerve rootlets, in some patients it remained localized to the spine itself. In some individuals, moderate amounts of opiates served to relieve the pain, while in others only the intravenous use of procaine hydrochloride was efficacious. In several patients the pain presented a confusing clinical picture, and many radiologic examinations were carried out in an attempt to delineate the cause of the pain. In some of these, radiotherapy was directed to the spine, since it was presumed that the pain was caused by a tumor mass pressing on the nerve

rootlet; none of these cases was helped by the treatment. Other patients presented with complaints of epigastric distress suggestive of cholecystitis or peptic ulcer. Because steroids had been administered for the primary disease, peptic ulcer was strongly suspected. The following case is an excellent example of the diagnostic and therapeutic problem which herpes zoster may present in these situations.

#### CASE REPORTS

*Case 9.* A 34 year old white male warehouseman had Hodgkin's disease diagnosed in June, 1956, by cervical lymph node biopsy. When first seen, he had generalized itching, a weight loss of 12 pounds, and massive enlargement of cervical nodes, producing a "bull-neck" appearance. Other regional lymph nodes were involved, but there was no splenomegaly or hepatomegaly. Radiographic examination of the chest showed extensive mediastinal involvement. The patient was treated with cobalt teletherapy to the cervical and mediastinal areas. Three months later there was recurrence of right cervical adenopathy, and he was again treated with radiation. The development of pulmonary radiation reaction necessitated institution of steroids, and considerable improvement followed a course of methylprednisolone. In May, 1958, the patient began to complain of epigastric pain. No objective evidence of recurrence of disease could be found, and no other significant physical findings were noted. Although gastrointestinal radiographs were normal, he was given symptomatic treatment for peptic ulcer, without benefit. In June, a typical herpes zoster eruption occurred over the left lower chest and epigastrium, and the epigastric pain subsided. When the patient was seen three weeks later the herpetic eruption had healed, and he had no complaints. There was no further progression of the lymphomatous disease during follow-up observation for six months.

*Cranial Nerve Involvement:* While involvement of the cranial nerves is not uncommon in herpes zoster, the development of this complication in patients with hematologic neoplasias may present special problems. One of our patients with multiple myeloma complained bitterly of severe headache. Because he was known to have many large osteolytic lesions of the skull, it was assumed that his headache was related to the myelomatous involvement of the cranium, and local radiotherapy of the skull was planned to relieve the excruciating pain. However, before treatment could be instituted, a vesicular eruption appeared on the right forehead, and the diagnosis of herpes zoster of the fifth cranial nerve was established (figure 1). Involvement of the ophthalmic division of the fifth cranial nerve has been reported as a common finding in at least one series.<sup>11</sup>

*Case 20.* A 48 year old white male rancher with multiple myeloma that had first been diagnosed in January, 1956, was treated briefly with urethane and prednisolone, but without benefit. He was then started on chlorambucil, with subjective improvement. Because of a sudden drop in hematocrit in February, 1958, he was begun on prednisolone, 30 mg. daily, and the anemia improved. During prednisolone therapy he complained of severe, persistent right frontal headache, and eventually developed a typical herpetic eruption over the ophthalmic division of the trigeminal nerve. Two years later he developed thoracic herpes while taking steroids for hemolytic anemia. Radiographs showed collapse of the thoracic vertebrae in the region of the nerve rootlets involved.



FIG. 1. Herpes zoster of the ophthalmic division of the trigeminal nerve in a patient with multiple myeloma.

In some patients with relatively benign lymphomas, the occurrence of herpes zoster presented more distressing problems than did the underlying disease. This was well illustrated by the case of a woman with lymphocytic lymphosarcoma whose disease appeared to be inactive, but who developed herpes zoster of the geniculate ganglion (seventh cranial nerve). We are not aware of another case of Ramsay-Hunt syndrome<sup>5,6</sup> associated with lymphosarcoma.

*Case 11.* A 45 year old white female housewife had been found to have lymphocytic lymphosarcoma in April, 1955, when an enlarged cervical lymph node was biopsied. This was successfully treated with radiotherapy to various groups of enlarged nodes. In December, 1956, she was begun on chlorambucil therapy because of recurrence of generalized lymphadenopathy. She did well until March, 1957, when she developed fever, ulcerative pharyngitis, paresis of the right facial nerve (peripheral type), deafness on the right, and loss of taste. She also had pain and paresthesias of the right occipital and postauricular areas, the right shoulder and neck. Examination revealed herpetic lesions in the auditory canal, right cheek, temple, forehead and neck (figure 2). The corneal reflex was absent, and there was loss of taste on the right side of the tongue. There was no sensory loss in the face.

The patient was treated with massive doses of vitamin B<sub>12</sub> and prednisolone, without benefit, but some relief of pain was obtained with intravenous infusions of procaine. Following discharge she had prolonged convalescence, with partial



improvement in the facial paralysis and hearing deficit. Loss of taste and anesthesia of the pharynx continued, however, resulting in paroxysms of coughing. In addition, chronic otitis media developed secondary to the vesicular lesions of the auditory canal.

*Generalized Herpes:* Generalized herpes zoster associated with leukemia was reported as early as 1913.<sup>7</sup> By 1940, 34 additional cases had been reported in the literature, 29 associated with lymphocytic leukemia.<sup>8</sup> The development of herpetic lesions at various sites remote from the initial zone of distribution is apparently not rare, and has been variously estimated as being from 66%<sup>9</sup> to 90%.<sup>10</sup> On the other hand, at least one report revealed the incidence of generalized distribution to be only 2% in a series of 206 patients.<sup>11</sup> The term "herpes zoster generalisatus" has been applied to a rare manifestation of this viral infection in which large numbers of herpetic lesions have widespread distribution over the body in addition to the classic nerve rootlet distribution. In some patients the distribution of the lesions is suggestive of varicella, and a relationship between the virus of herpes zoster and varicella has been considered.<sup>12, 13, 14, 15</sup> There have been reports of herpes zoster developing in adults while a child in the household had chickenpox.<sup>16</sup> Similarly, chickenpox has been observed to occur after contact with herpes zoster.<sup>17</sup>

*Case 14.* A 54 year old white male with lymphocytic lymphosarcoma was treated with radiotherapy, with good subjective and objective improvement. Two years later he was treated with triethylene melamine (TEM) and nitrogen mustard



FIG. 2. Ramsay-Hunt syndrome developing in a patient with lymphocytic lymphosarcoma. Note the typical facial palsy (left) and a large bullous lesion of the ipsilateral external auditory canal (right).



FIG. 3. "Herpes zoster generalisatus" in a patient with terminal lymphocytic lymphosarcoma (left). The original skin lesions appeared over the right sacral and gluteal regions, but eventually spread to form a coalescent hemorrhagic eruption of the abdomen (right), with discrete "satellite" lesions over the rest of the body.

on two separate occasions. There was no objective improvement, and the disease progressed, with the eventual development of the clinical picture of "leukosarcoma" (white blood cell count, 23,700). He became acutely ill with anemia and generalized anasarca, and developed a hemorrhagic herpetic eruption over the right sacral and gluteal region. Despite treatment with blood transfusions, prednisolone and chlorambucil, he continued a downhill course. The herpetic eruption became more diffuse and spread over the entire abdomen (figure 3). Later a discrete, papulopustular generalized rash developed which clinically resembled chickenpox. The patient died from a severe necrotizing pneumonia.

While definite "satellite" vesicles were observed in four of our patients, true generalization was seen in two of these cases in the terminal phase of lymphosarcoma and Hodgkin's disease. It is important to note that all of these patients were receiving steroid therapy at the time they developed the herpetic lesions. The case to be reported received massive doses of prednisolone.

*Case 2.* A 19 year old white male was found to have Hodgkin's disease in 1950, when an enlarged cervical node was biopsied. He received radiation therapy to the neck and mediastinum in March, 1953. In February, 1955, he developed low back pain, radiating down the legs. Spinal fluid examination revealed an abnormal colloidal gold curve and a positive Pandy test. Radiotherapy was directed toward the spinal cord segment suspected to be involved by the lymphoma, and the patient improved. Over a period of six months he developed paralysis of the lower extremities. Nitrogen mustard therapy effected temporary improvement. When symptoms recurred, he received more intensive treatment with cobalt teletherapy. By August, 1956, he was able to stand in a walker and to take a few steps. Therapy

with chlorambucil, 12 mg. daily, was begun at this time, and he continued to improve. He was discharged from the hospital in mid-September.

In October, 1956, the patient was admitted to the hospital because of progressive weakness, itching of the skin, bizarre mental symptoms, slurred speech and jaundice. The neck was stiff, and positive Brudzinski and Kernig signs were elicited; spinal fluid examination was normal. The patient was given blood transfusions, cobalt teletherapy to the base of the skull, and intravenous nitrogen mustard, without benefit. The progressive downhill course continued. He was given massive doses of prednisolone (800 mg.) for two days, following which he developed discrete disseminated pustular lesions resembling varicella. He died two days later.

*Paralysis:* Muscular weakness and paralysis are not common complications of herpes zoster. However, a number of cases have been reported exhibiting flaccid paralysis, with absence of the deep tendon reflexes and some degree of atrophy. When an upper extremity is involved, the pain may cause prolonged immobilization of one arm, resulting in fixation of the shoulder joint and edema of the arm.<sup>16</sup> We have observed this complication in one patient.

*Case 12.* A 77 year old white female with lymphocytic lymphosarcoma presented with generalized lymphadenopathy, marked splenomegaly, hepatomegaly, ascites and peripheral edema. She was treated with chlorambucil, 8 mg. daily, digitalis, and mercurial diuretics. An initial white blood count of 22,000, with 62% lymphocytes, returned to normal after four months of therapy. There were a reduction in lymphadenopathy and slight reduction in splenomegaly and hepatomegaly. The patient was continued on maintenance doses, and one month later developed herpes zoster of the right arm and shoulder. She was treated with vitamin B<sub>12</sub>, 1,000 µg. intramuscularly, at frequent intervals. The vesicular eruption cleared promptly but severe neuralgia persisted. In addition, she developed weakness of the muscles of the right shoulder girdle and arm. She was treated with intravenous procaine infusions, and obtained prompt and fairly complete relief of the neuralgia, though the weakness of the muscles persisted.

*Postherpetic Neuralgia:* Although this complication rarely occurs in individuals under the age of 40,<sup>3</sup> it presented a serious problem to us, since many of our patients belonged in the older age category. Following the initial skin eruption, 14 patients complained of persistent pain which lasted from 10 days to nine months. While a number of therapeutic agents were utilized in an attempt to hasten healing and alleviate the pain (steroids, massive doses of vitamin B<sub>12</sub>, Protamide), we found that the intravenous administration of 500 c.c. of 0.1% procaine hydrochloride in normal saline for three or four days was the most effective means of relieving pain.<sup>18</sup>

*Case 4.* A 43 year old white female housewife had an extradural tumor excised in the lumbar region in March, 1957. Histologic study of the tissue was considered to be diagnostic of Hodgkin's disease. Her general physical condition was good. She received radiotherapy postoperatively, and a total dosage of 500r was delivered to the lumbar spine area. One week following completion of the radiotherapy she developed herpes zoster, with segmental distribution of the seventh intercostal nerve on the left. Chest x-ray examination at the time was considered to be normal. There was considerable pain associated with the herpetic lesions. This lasted for a

period of 10 months, at which time the patient was first seen at the City of Hope Medical Center (January, 1958). In the interval there were recurrences of small crops of vesicles appearing on the skin of the lower anterior chest and abdomen. Radiographic examination of the chest in January, 1958, revealed a mass posteriorly adjacent to the transverse process of T10. Part of the tenth and eleventh ribs, as well as the transverse process of the tenth dorsal spine, was destroyed by the tumor. Because of the persistent postherpetic neuralgia, the patient was given procaine hydrochloride solution intravenously for four consecutive days, with good relief of pain.

### DISCUSSION

While it is generally accepted that herpes zoster may exist as a primary disease caused by a specific filtrable virus, the pathogenesis of herpes zoster secondary to other disease processes is not entirely clear. Apparently the disorder may result from pressure or trauma to the nerve rootlets, since herpes zoster has been reported following injury to the spine<sup>19</sup> and in association with an intradural cyst.<sup>20</sup> Herpes zoster may be associated with arsenic poisoning.<sup>21</sup> As early as 1865, herpes zoster was observed to have developed from metastatic carcinoma to the spine.<sup>22</sup> A number of excellent papers have been published on the pathologic findings of herpes zoster associated with the lymphomas and leukemias.<sup>19, 23, 24, 25, 26</sup> All of these authors found neoplastic invasion of the spinal ganglia and posterior roots paralleling the distribution of the herpetic lesions. On the other hand, other investigators have observed leukemic or tumor involvement of cranial and spinal nerves without an associated herpes zoster.<sup>27, 28</sup> The fact that herpes zoster apparently occurs more frequently in lymphomas than in any other neoplastic disorder,<sup>1</sup> and is a common complication of chronic lymphocytic leukemia but rare in the granulocytic form,<sup>2</sup> suggests a relationship between lymphoid tissue and the virus infection. In recent years a number of studies have confirmed the fact that chronic lymphocytic leukemia and lymphosarcoma may be associated with a deficiency of gamma globulin.<sup>29, 30, 31, 32</sup> It is possible, then, that the lack of gamma globulin antibody in these patients makes them much more susceptible to viral infections. Similarly, this defect in immunity might explain the tendency for herpes to become generalized in patients with chronic lymphocytic leukemia. While there appears to be good evidence that immune mechanisms may be impaired in Hodgkin's disease,<sup>33</sup> the defect does not appear to involve the properdin system.<sup>34</sup>

The relationship of the onset of herpes zoster to therapy would appear to be of more than casual interest. All except four patients, two of whom had chronic granulocytic leukemia, had received one or more therapeutic measures prior to or at the time herpes zoster appeared. The majority of these patients were in good general condition, and a number had only localized disease. Many of the patients developed their lesions at the site of radiotherapy. Radiotherapy, alkylating agents and steroids have in common the ability to suppress immune mechanisms, and it would appear reason-

able to assume that the herpes virus could become "active" or invasive following treatment. In the case of radiation, treatment of regional tumor masses produces local tissue injury which might result in defective local antibody formation. Loss of body protein is known to occur following use of ionizing radiation.<sup>35</sup> The fact that all the patients who developed disseminated herpetic lesions were on steroids was emphasized above.

There is some evidence to suggest that herpetic eruptions may be produced by manipulation of the nerve root during such operative procedures as rhizotomy or retrogasserian neurectomy.<sup>16</sup> In addition, intraspinal tumors may irritate posterior roots and produce herpetic lesions in the distribution of the nerve.<sup>36</sup> In the large series of patients reported from Memorial Center (162 patients),<sup>4</sup> it was observed that 68% of the cases had clinical evidence of active tumor at the same level and time that the herpes occurred. There was a fourfold increase in the incidence of herpes when spinal cord compression occurred. From this evidence the authors concluded that herpes zoster "may be precipitated by tumor involvement at any point in the afferent portion of the reflex arc." An excellent study of the pathologic changes occurring in the dorsal root ganglia and adjacent nerves in hematologic neoplasias was reported by Dickenman and Chason.<sup>37</sup> Of 93 cases studied, cellular infiltrations involving the peripheral nerves, central nerve roots and spinal ganglia were observed in 66. These were of a nonspecific nature in 39, and probably specific neoplastic invasion in 27 cases. Unfortunately, the pathologic changes observed were not correlated with known neurologic involvement in these patients, and there was no mention of the occurrence of herpes zoster. In spite of all of the investigative work that has been done, the mechanisms by which vesicles form on the skin as a result of nerve root or ganglion stimulation are still obscure.

#### SUMMARY

The literature concerning the association of herpes zoster and malignant disease has been briefly reviewed. Twenty-four additional cases of herpes zoster associated with leukemias and lymphomas are reported. Salient clinical findings are discussed and certain unusual manifestations are emphasized, notably the development of Ramsay-Hunt syndrome in a case of lymphosarcoma. The various theories concerning the pathogenesis of herpes zoster secondary to other disease processes are presented, and the role of defective immune mechanisms is emphasized. Treatment with radiation, alkylating agents and corticosteroids preceded the development of herpes zoster in 20 of the cases reported, and it is suggested that these agents may increase susceptibility to herpes zoster.

#### ACKNOWLEDGMENT

The authors wish to acknowledge the help of Leath Bracken in collecting and coordinating the data upon which this paper is based.

## SUMMARIO IN INTERLINGUA

Le litteratura concernente le association de herpette zoster e morbo maligne es revistate brevemente. Vinti-quatro casos additional es reportate.

Le protocollas medical de 475 patientes con varie dyscrasias del sanguine esseva scrutinate pro le occurrentia de herpette zoster. Inter 303 patientes con chronic leucemia, lymphoma, o myeloma, 24 (i.e. 7,9%) disveloppava herpette zoster al un o al altere tempore durante le curso de lor morbo. Illo occurreva le plus frequentemente in patientes con morbo de Hodgkin. Illo non se disveloppava in ulle del 81 patientes con leucemia acute.

Dolores—manifeste inter plure dies a plure septimanas ante le disveloppamento del lesiones cutanee—esseva le plus uniforme e etiam le plus confudente inter le symptomas notate. Affection del nervo cranial non esseva incommun e presentava problemas special. Un patiente con lymphosarcoma lymphocytic disveloppava le syndrome de Ramsay-Hunt. Herpette zoster de forma generalisate esseva observate in solmente quatro del casos studiate, e un extense dissemination esseva evidente in solmente duo del quatro. Paralyse esseva observate in un patiente. A causa del avantiate etate de multes del patientes studiate, le incidentia de neuralgia postherpetic esseva alte (14 casos) e presentava un serie problema.

Le facto que herpette zoster occorre plus frequentemente in lymphoma que in ulle altere disordine neoplastic e que illo es commun como complication de chronic leucemia lymphocytic sed rar in le forma granulocytic de iste condition suggere un relation inter tissu lymphoide e le infection viral. Il es possibile que defective mecanismos immunologic in tal casos augmenta le susceptibilitate pro herpette zoster.

Le relation inter le declaration de herpette zoster e le therapia es de interesse special. Tractamento con radiation, agentes alcoylante, e corticosteroides precedeva le disveloppamento de herpette zoster in 20 del casos reportate.

## BIBLIOGRAPHY

1. Craver, L. F., and Haagensen, C. D.: A note on the occurrence of herpes zoster in Hodgkin's disease, lymphosarcoma and the leukemias, *Am. J. Cancer* **16**: 502-514, 1932.
2. Ferreira, M. J.: Herpes zoster generalisatus bei Leukämie, *Arch. f. Dermat. u. Syph.* **176**: 295-308, 1937.
3. De Moragas, J. M., and Kierland, R. R.: The outcome of patients with herpes zoster, *Arch. Dermat.* **75**: 193-196, 1957.
4. Williams, H. M., Diamond, H. D., and Craver, L. F.: The pathogenesis and management of neurological complications in patients with malignant lymphomas and leukemias, *Cancer* **11**: 76-82, 1958.
5. Harrison, K., Spillane, J. T., Monkhouse, J. P., Harris, W., Punt, N. A., Laskiewicz, A., and Cawthorne, T.: The Ramsay-Hunt syndrome, a discussion, *Proc. Roy. Soc. Med.* **47**: 371-384, 1954.
6. Findlay, J. P.: Facial paralysis: a clinical review with an autopsy report of the histopathology in a case of infection of the geniculate ganglion by the virus of cephalic herpes zoster, *M. J. Australia* **2**: 810-815, 1952.
7. Fischl, F.: Herpes zoster generalisatus bei Leucaemia lymphatica, *Arch. f. Dermat. u. Syph.* **118**: 553, 1913.
8. Wile, U. J., and Holman, H. H.: Generalized herpes zoster associated with leukemia, *Arch. Dermat. and Syph.* **42**: 587-592, 1940.
9. Bluefarb, S. M., and Morris, G. E.: Herpes zoster with aberrant vesicles: report of 20 cases, *Arch. Dermat. and Syph.* **43**: 385, 1941.
10. Tenneson, H.: *Traite clinique de dermatologie*, 1893, O. Doin, Paris, p. 116.
11. Burgoon, C. F., Burgoon, J. S., and Baldrige, G. D.: The natural history of herpes zoster, *J. A. M. A.* **164**: 265-269, 1957.



12. Kundratitz, K.: Experimentelle Uebertragungen von Herpes zoster auf Menschen und die Beziehungen von Herpes zoster zu Varicellen, *Ztschr. f. Kinderh.* **39**: 379-387, 1925.
13. Bruusgaard, E.: Mutual relation between zoster and varicella, *Brit. J. Dermat.* **44**: 1-24 (Jan.) 1932.
14. Rake, G., Blank, H., Coriell, L. L., Nagler, F. P. O., and Scott, T. F. M.: The relationship of varicella and herpes zoster: electron microscope studies, *J. Bact.* **54**: 293, 1948.
15. Welle, T. H.: Serial propagation in vitro of agents producing inclusion bodies derived from varicella and herpes zoster, *Proc. Soc. Exper. Biol. and Med.* **80**: 340, 1953.
16. Grinker, R. R., and Bucy, P. C.: *Neurology*, 4th Ed., 1949, Charles C Thomas, Springfield, Illinois, p. 651.
17. Von Bokay, J.: Ueber den ätiologischen Zusammenhang der Varizellen mit gewissen Fällen von Herpes zoster, *Wien. klin. Wchnschr.* **22**: 1323-1326, 1909, quoted by van Rooyen, C. E., and Rhodes, A. J.: *Virus diseases of man*, 1948, Thos. Nelson and Sons, New York, p. 163.
18. Shanbrom, E.: Unpublished data.
19. Head, H., and Campbell, A. W.: The pathology of herpes zoster and its bearing on sensory localization, *Brain* **23**: 353-523, 1900.
20. Kamman, G. R.: Herpes zoster as an early symptom of spinal cord tumor, *J. A. M. A.* **91**: 320, 1928.
21. Jacob, F. M.: Bilateral herpes zoster following acute arsenic poisoning, *Arch. Dermat. and Syph.* **24**: 280, 1931.
22. Charcot, J. M., and Cotard, J.: Sur un cas de Zone du Cou, *Compt. rend. Soc. de biol.* **17**: 41-48, 1865.
23. Morton, H. H. P.: A case of herpes zoster apparently due to invasion of the ganglia by round cell sarcoma, *J. Neurol. and Psychopath.* **6**: 296, 1926.
24. Fahr, T.: Kurzer Beitrag zur Frage des Herpes zoster, *Dermat. Wchnschr.* **64**: 285, 1917.
25. Freund, H.: Zoster und Leukämie, *Arch. f. Dermat. u. Syph.* **145**: 476, 1928.
26. Freund, H.: Zoster generalisatus und Leukämie, *Dermat. Wchnschr.* **88**: 375, 1929.
27. Trommer, E., and Wohlwill, F.: Über Erkrankungen des Nervensystems, insbesondere der Hirnnerven, bei Leukämie, *Deutsche Ztschr. f. Nervenhe.* **100**: 233, 1927.
28. Kerch, E.: Kenntnis der Neurinome bei Recklenghausenscher Krankheit, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **74**: 379, 1922.
29. Jim, R. T. S.: Serum gamma globulin levels in chronic lymphocytic leukemia, *Am. J. M. Sc.* **234**: 44-47, 1957.
30. Wall, R. L., Sun, L., and Picklow, F. E.: Serum proteins in diseases of the reticulo-endothelial system; the significance of hypogammaglobulinemia, *RES Bull.* **2**: 50-53, 1956.
31. Hudson, R. P., and Wilson, S. J.: Hypogammaglobulinemia and chronic lymphocytic leukemia, *J. Lab. and Clin. Med.* **50**: 829-830, 1957.
32. Shanbrom, E.: Unpublished data.
33. Schier, W. W., Roth, A., Ostroff, G., and Schrift, M. H.: Hodgkin's disease and immunity, *Am. J. Med.* **20**: 94-99, 1956.
34. Rottino, A., Levy, A. L., and Bianco, A.: Serum-properdin levels in patients with Hodgkin's disease and carcinoma, *Cancer* **10**: 877-883, 1957.
35. Greenberg, J., and Laszlo, D.: The influence of ionizing radiation on the body composition of patients with malignant lymphoma, *J. Lab. and Clin. Med.* **49**: 514-525, 1957.
36. Bucy, P. D., and Buchanon, D. N.: Teratoma of the spinal cord, *Surg., Gynec. and Obst.* **60**: 1137, 1935.
37. Dickenman, R. C., and Chason, J. L.: Alterations in the dorsal root ganglia and adjacent nerves in the leukemias, the lymphomas and multiple myeloma, *Am. J. Path.* **34**: 349-361, 1958.

## PULMONARY CRYPTOCOCCOSIS: TREATMENT WITH AMPHOTERICIN B \*

By JOHN R. DURANT, Lieutenant (MC) USNR, LEONARD D. EPIFANO,  
Lieutenant (MC) USNR, and SIMON W. EVER, Captain (MC)  
USN, Charleston, South Carolina

Most physicians and medical students tend to think of clinical infection with *Cryptococcus neoformans* as a rare form of meningitis which serves as the *coup de grâce* for a few patients suffering from malignant lymphomas. A few brief paragraphs are devoted to it in most standard bacteriologic and medical textbooks. Lecturers generally mention the subject only in passing. Discovery of a patient suffering from cryptococcosis is thus a surprise to most physicians, and the event is heralded as a rarity.

*C. neoformans* as a cause of disease is probably less rare than is thought. In the United States, about 50 deaths a year are attributed to this cause, but the figure is probably artificially low because of inadequate reporting and diagnostic errors.<sup>1</sup> Fitzpatrick et al. reported the discovery of four cases of cryptococcal meningitis in a period of one and a half years. During this time, only one case of tuberculous meningitis was encountered.<sup>2</sup> There is an ever increasing number of case reports and discussions of the problem, attesting to the frequency with which this entity is being encountered. One group of authors was able to find as many as 21 cases in one institution in a period of 11 years.<sup>3</sup> Reports of smaller but still appreciable numbers are common.<sup>4-10</sup>

Because of its dramatic clinical picture, meningitis has been the form most frequently recognized. The increasing number of reports of pulmonary cryptococcosis makes it apparent that there is frequently a respiratory phase which precedes the appearance of meningitis, sometimes by many years.<sup>3, 5, 7, 9, 11-13</sup> Most authors believe that the lungs are the usual portal of entry. Certainly the pulmonary form is not rare. White and Arany reviewed 310 cases and found that at least 100 had had clinical manifestations of pulmonary disease at some time during the course of the illness.<sup>14</sup> Of 21 cases reported from Los Angeles County Hospital, 14 had pulmonary foci.<sup>3</sup> The majority of these patients with pulmonary disease eventually succumbed to generalized cryptococcosis.

In 1956 the discovery of a broad-spectrum antifungal antibiotic, amphotericin B, opened a new horizon in mycology. Since that time a number of reports have appeared which have established this drug as the most effective

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From the Department of Medicine, U. S. Naval Hospital, Charleston, South Carolina.

Requests for reprints should be addressed to John R. Durant, M.D., Temple University Hospital, Broad and Ontario Streets, Philadelphia, Pennsylvania.

known agent against most systemic mycoses, including cryptococcosis.<sup>1, 2, 8, 15-17</sup> The availability of effective therapy for cryptococcosis now makes it imperative for the average practitioner to familiarize himself with this disease. Because of this we believe that a report of three cases, two successfully treated with amphotericin B, is of value.

#### CASE REPORTS

*Case 1.* A 52 year old white male was admitted to the U. S. Naval Hospital, Charleston, South Carolina, on March 17, 1959, because of dyspnea, weight loss and a chronic cough of three weeks' duration. The patient denied previous respiratory disease. Physical examination revealed an asthenic white male who appeared to be both acutely and chronically ill. Blood pressure, 90/68 mm. of Hg; pulse, 110;

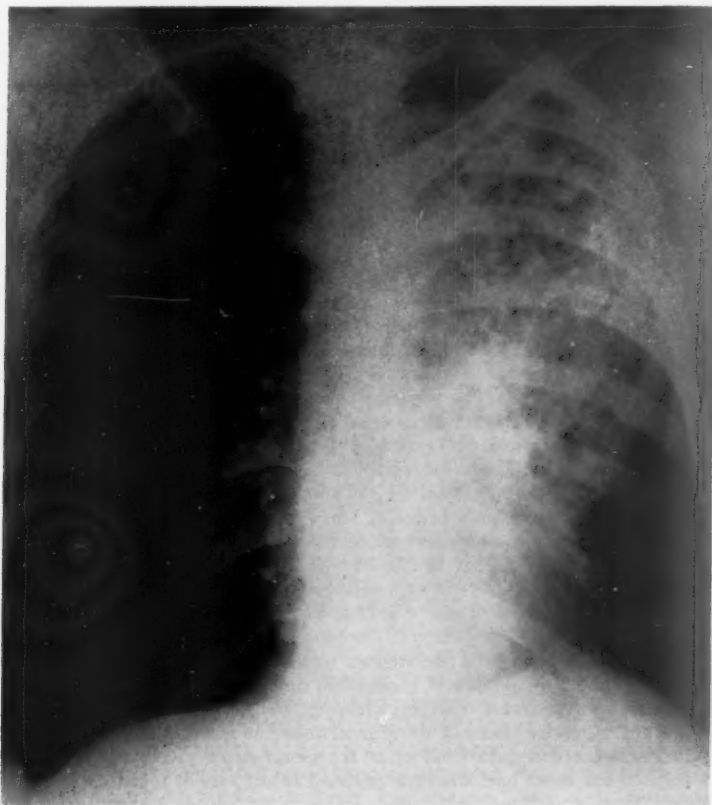


FIG. 1. *Case 1.* Posterior-anterior chest film (3/26/59) shows a diffuse, consolidated infiltration involving the entire left upper lobe, with interspersed areas of relative radiolucency which suggest cystic changes secondary to obstructive phenomena. There is no evidence of pleural reaction, and the remaining lung fields appear clear. The clouding in the costophrenic angles is due to artifactual shadows on the film.

respiration, 24; temperature, 97.6° F. The pertinent physical findings included clubbing of the fingers, and the presence of coarse, crepitant râles which were audible over the left anterior chest. The chest roentgenogram on admission (figure 1) was interpreted by the radiologist as consistent with left upper lobe pneumonia. However, because of the finding of multiple radiolucencies, pulmonary tuberculosis was also considered to be a strong possibility. In view of the radiologic findings and the gravity of the patient's condition, both antibacterial and antituberculous therapy were instituted. A repeat chest film, made on the fifth hospital day, was interpreted as resolving bacterial pneumonia, but the patient's clinical course did not parallel the improvement demonstrated in the x-rays. Skin tests for histoplasmosis, blastomycosis and coccidioidomycosis were all negative. Skin tests with purified protein derivatives (first and second strength) were negative. On the tenth hospital day, *Cryptococcus neoformans* was cultured from the patient's sputum. He was then placed on Amphotericin B\* intravenously, in increasing increments of 10 mg. daily, until a total dose of 1 mg. per kilogram of body weight was obtained. The vehicle of administration was 5% dextrose in water in a dilution of 1 mg. of amphotericin B to 10 c.c. of diluent. The patient was continued on 75 mg. of amphotericin B in 1,000 c.c. of glucose and water on alternate days from March 27 to May 15, 1959, a total of seven weeks. Side reactions included isolated episodes of chills and fever, nausea, occasional vomiting, and localized phlebitis and cellulitis at the site of administration. All of the side reactions were either self-limiting, or well controlled by parenteral antihistaminics, except for the localized reaction at the sites of the amphotericin infusions. This complication was present only while the drug was being administered, and constituted the primary reason for temporarily discontinuing the medication after a period of seven weeks. Little or no improvement was obtained from the use of local applications of heparin and Dicumarol. On May 18, 1959, three days after the discontinuance of the amphotericin B, another culture was obtained which was positive for *C. neoformans*. Antifungal therapy was resumed, this time with the same dosage (75 mg.) of amphotericin B, but with twice the amount of diluent, given on alternate days. However, because of severe pain and phlebitis at the sites of infusion, it was impossible to continue the patient on therapy for longer than seven to 10 days. On the other hand, discontinuing therapy resulted in almost immediate appearance of positive cultures. This perplexing problem was solved by the administration of 1 c.c. of 1% procaine directly into the intravenous tubing every hour. This achieved complete control of the localized reaction, and permitted the administration of 100 mg. of amphotericin B in 1,000 c.c. of dextrose in water on alternate days for a period of six weeks, during which time daily fungus cultures of the patient's sputum were negative. It was necessary to discontinue the drug during the later course of therapy for periods of two to four days because of the appearance of azotemia (blood urea nitrogen, 48 mg.%).

Serial roentgenograms of the chest demonstrated progressive clearing of the left upper lobe infiltrate, with anterior displacement of the greater fissure, and shift of the mediastinal contents and the trachea to the left, suggesting decreased volume of the left upper lobe. Subsequent films taken during the latter part of the patient's hospitalization demonstrated further clearing of the left upper lobe infiltrate and return of the greater fissure to the normal anatomic position (figure 2). Although the cultures remained negative following the cessation of therapy, surgical removal of the diseased left upper lobe was recommended to the patient because of the previous appearance of positive fungus cultures. This was refused, and shortly thereafter he left the hospital against medical advice.

*Case 2.* A 29 year old Negro male was admitted to the U. S. Naval Hospital in Charleston on September 19, 1956, because of a mild cough productive of small

\* Supplied as Fungizone by Squibb & Sons, New York.

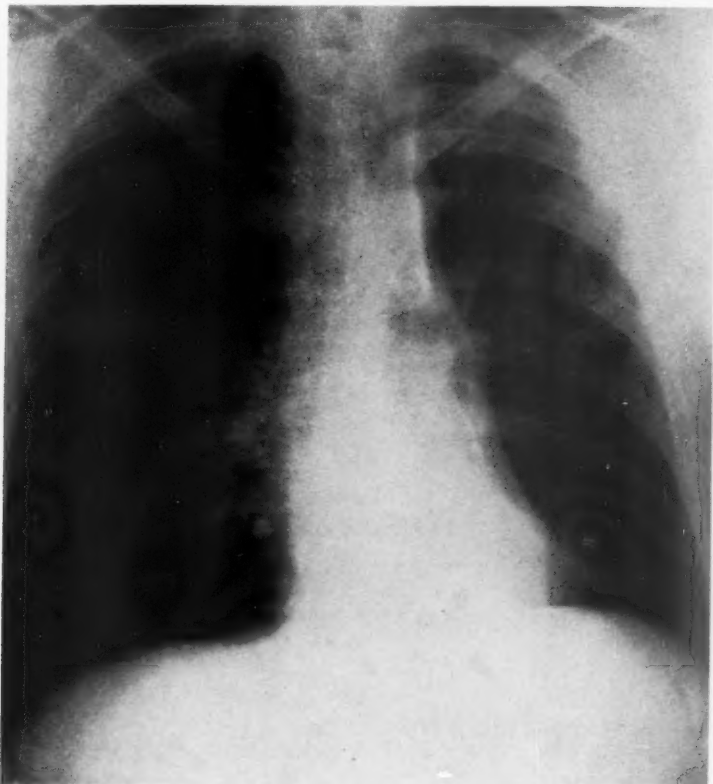


FIG. 2. *Case 1.* Posterior-anterior chest film (7/1/59) shows almost complete interval clearing of the infiltrative process in the left upper lobe. The only residual consists of some heavy fibrotic markings radiating in striae from the left superior hilar region. The remainder of the chest continues to be unremarkable.

amounts of whitish sputum, weakness, and severe headache of one week's duration. During this time he had had intermittent fever as high as  $104^{\circ}$  F.

Physical examination revealed an alert, oriented Negro male who appeared to be acutely ill and who complained of severe frontal headache. The only significant physical finding was that of minimal nuchal rigidity. Roentgenogram of the chest on admission revealed a circumscribed lesion in the right lower lobe (figure 3). A lumbar puncture was performed on the day of admission. The opening pressure was 370 mm.; closing pressure, 190 mm. The spinal fluid was clear. There were 386 cells, with an equal distribution of neutrophils and lymphocytes. The sugar was 59 mg. and the total protein, 20 mg. Culture of the spinal fluid for tubercle bacilli was negative. Skin tests for blastomycosis, histoplasmosis and coccidioidomycosis were negative. Skin test for tuberculosis, however, was positive. An initial India ink preparation on the spinal fluid was negative, but a repeat determination revealed capsulated spherical forms which were considered to be highly suggestive of *C. neoformans*.

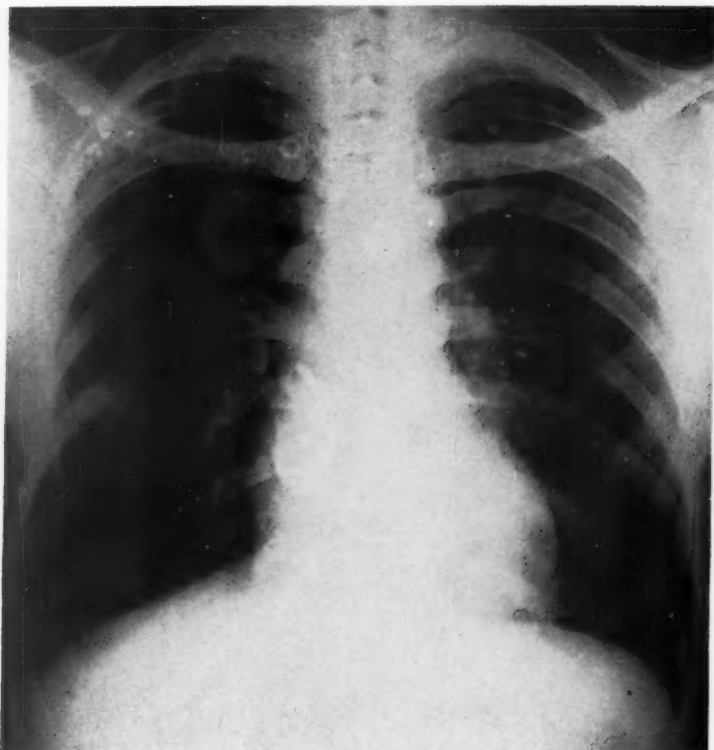


FIG. 3. Case 2. Posterior-anterior chest film (9/10/56) shows an area of increased radiopaque density, measuring some 3 cm. in greatest diameter, projecting into the superior segment of the right lower lobe. It is rather sharply demarcated, however, the margins are somewhat ragged and irregular. There is no evidence of significant parenchymal reaction around the periphery of the lesion, but there is a suggestion of striae radiating to the right hilar region. No detectable pleural change is visible. The remaining lung fields are clear.

On the twenty-second hospital day a growth was obtained on Sabouraud's medium which was considered to be compatible with *C. neoformans*. This was subsequently corroborated by the performance of a virulence test on mice. Repeated lumbar punctures during the course of the patient's hospitalization consistently demonstrated an elevated spinal fluid pressure, normal protein and sugar, and an elevated cell count, ranging from 100 to 600, with a predominance of lymphocytes. There was no significant radiographic change in the circumscribed lesion of the right lower lobe throughout the period of the patient's hospitalization. His initial therapy consisted of large doses of aqueous penicillin, streptomycin, salicylates, and opiates for severe headache. On the eighteenth hospital day, because of the clinical suspicion of tuberculous meningitis, isonicotinic acid hydrazide, para-aminosalicylic acid and pyridoxine were added. On the twenty-second hospital day, because of the isolation of the cryptococcal organisms, all antibacterial and antituberculous medication was discontinued. Therapy consisting of 6 gm. of sulfadiazine in divided doses and 600



mg. of sodium bicarbonate four times daily, was then instituted. Large doses of parenteral aqueous penicillin daily were added on the twenty-fourth hospital day. On the forty-first hospital day the patient was started on a total dose of 120 mg. of intravenous Actidione daily. Three days later the dosage was increased to 180 mg. daily. The final therapeutic attempt was that of intramuscular polymyxin B, which was begun on the morning of the patient's death. With the exception of short-lived improvement after the use of Actidione, the patient demonstrated no response to therapy, and presented a clinical picture of persistent headaches, low grade fever and increasing nuchal rigidity, with disorientation and progressive depression of the sensorium and coma. He died on the fifty-ninth hospital day. The postmortem examination revealed cryptococcal meningitis with hydrocephalus, areas of cryptococcal liquefaction necrosis in the brain, herniation of the cerebellum into the foramen magnum, and cryptococcal pneumonitis.

*Case 3.* This 46 year old white male was admitted to the hospital because of hemoptysis. He gave a history of many years of chronic cough, productive of from 100 to 200 c.c. of mucoid sputum daily. He had been bronchoscoped elsewhere several years before and told that the results were negative. Five days prior to admission there were an increase in the cough and the appearance of right-sided pleural pain and chills and fever. On the day of admission the patient had an episode of hemoptysis, because of which he sought admission. The past history was sig-

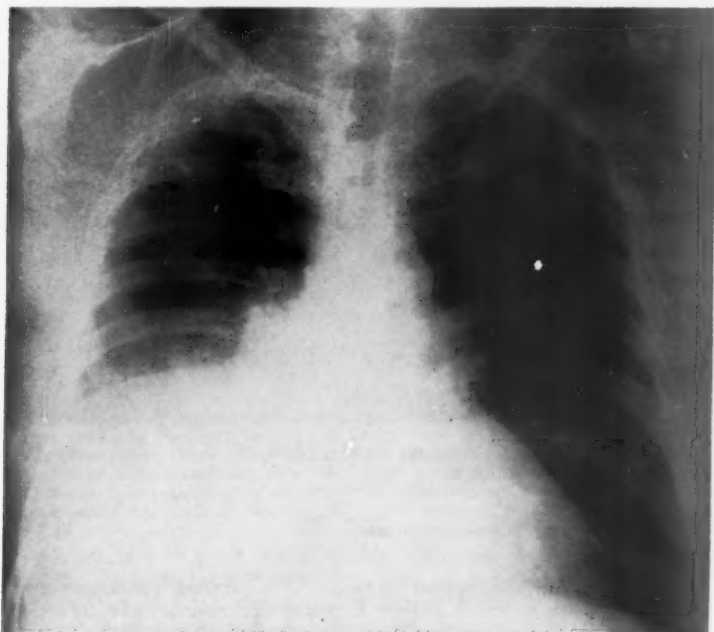


FIG. 4. *Case 3.* Posterior-anterior chest film (8/16/58) shows a diffuse clouding overlying the right lower lung field, which fades superiorly into a normal parenchymal lung pattern. On the lateral view, this was shown to be due to a pleural effusion. There is also pleuritic reaction in the right apex and along the right lateral thoracic wall. No distinct parenchymal infiltration is visible, except for some fibrotic, strandlike densities projecting in the right apex. The left lung field is unremarkable.

nificant in that he reported that for many years he had been informed of a stable right upper lobe infiltrate, thought to be healed tuberculosis.

Physical examination revealed a well developed, obese white male in respiratory distress. Blood pressure, 135/80 mm. of Hg; pulse, 130; temperature, 102.6° F. There were crepitant and sonorous râles at the right posterior lung base, as well as signs of a pleural effusion in the same area. The examination was otherwise unremarkable.

Laboratory data revealed the white blood count to be 15,300, with 80% polymorphonuclear cells. Sputum cultures for acid-fast bacilli were negative. On the

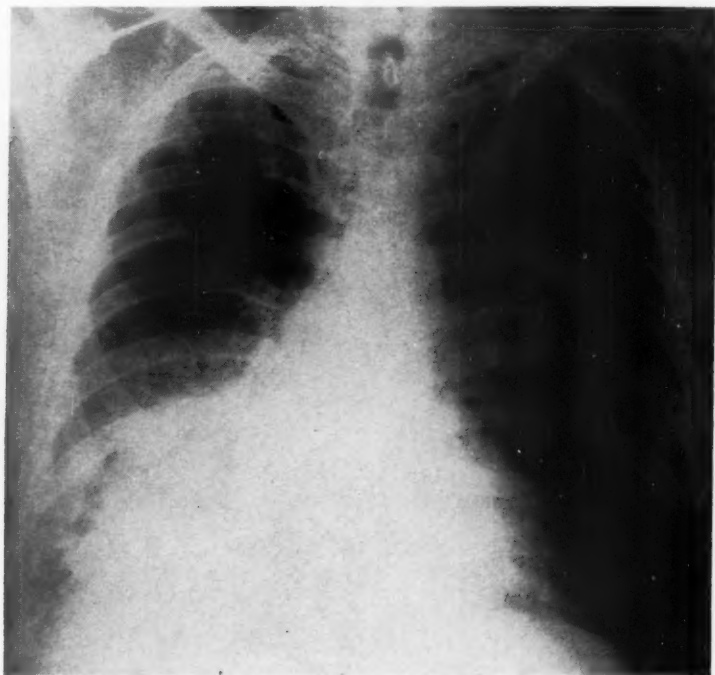


FIG. 5. Case 3. Posterior-anterior chest film (8/19/58) shows slight interval decrease in the quantity of pleural effusion at the right base, with radiolucent areas of apparent lung parenchyma visible through the clouding. It is difficult to evaluate the presence of parenchymal infiltration in the right lower lobe. The process at the right apex persists unchanged, and the left lung field remains clear.

third hospital day a growth compatible with *C. neoformans* was demonstrated on fungus cultures of the sputum. India ink preparation revealed the presence of an encapsulated, budding yeast. Subsequently, *C. neoformans* was cultured on numerous occasions from the patient's sputum and his gastric washings. Roentgenogram of the chest on admission demonstrated a pleural effusion of moderate extent at the right base, and an infiltrate in the second right anterior interspace (figure 4). Repeat examination on the fourth hospital day revealed a decrease in the pleural effusion, and visualization of an underlying infiltrative process involving the basilar segments

of the right lower lobe (figure 5). The effusion was tapped twice. On each occasion 500 c.c. of amber-colored sterile fluid, with the characteristics of an exudate, were removed.

The initial therapy consisted of streptomycin and penicillin, but with the isolation of *C. neoformans*, treatment with amphotericin B was instituted. The patient received a total of 2,875 mg. intravenously over a period of nine weeks, with a dosage schedule of 1 mg./Kg. (100 mg.) in 1,000 c.c. of 5% dextrose and water on alternate days until the seventh week, when transient azotemia (blood urea nitrogen, 20 to 35 mg.%) developed. A reduction in the dose of amphotericin B to 0.75 mg./Kg.



FIG. 6. Case 3. Posterior-anterior chest film (10/17/58) shows complete interval clearing of the process in the right lower lung field, with the residual consisting of some pleuritic scarring in the right costophrenic angle, right lateral thoracic wall, and just above the right diaphragm. The process at the right apex persists unchanged, and the left lung field remains unremarkable.

resulted in a return of the blood urea nitrogen to normal. In addition to azotemia, other side-effects were noted, including repeated episodes of thrombophlebitis at the site of administration, and occasional episodes of nausea and fever, controlled by slowing the rate of administration. The patient gradually improved, to the point where after two weeks of therapy he was able to carry on normal activity without difficulty. At this time, fungus cultures of the sputum were negative and remained so. Radiographically the right lower lobe infiltrate gradually cleared, with only minimal infiltrative changes and pleural thickening remaining (figure 6). The patient was advised to have removal of the right lower lobe, but the recommendation was refused. He was discharged at his own request.

## DISCUSSION

*C. neoformans* is an oval or spherical budding fungus which, in vivo, is surrounded by a thick, gelatinous capsule. The capsule is responsible for the characteristic appearance of the fungus when seen on a slide flooded with India ink. *C. neoformans* is easy to culture, especially on blood agar, at both 20° C. and 37° C. The colonies which appear in a few days to a few weeks are mucoid and white at first. As the organisms reproduce they become more yeastlike, lose their capsules, and develop a darker color.

There are nonpathogenic strains. These usually fail to grow at 37° C., and do not produce disease when injected into white mice.<sup>18</sup> This is not invariable, however. Pathogenic strains which did not grow at 37° C.,<sup>19</sup> or which had a very low pathogenicity on inoculation studies,<sup>7</sup> have been reported. Very little is known about the immunology of the disease, and there is as yet no practical and acceptable serologic or skin test for cryptococcosis.<sup>6</sup>

The pathologic response of the host is extremely variable. The gross appearance may be one of a highly localized, well walled-off disease. On the other hand, a gelatinous mass with virtually no surrounding reaction is frequently found. The microscopic features are equally varied.<sup>18</sup> The only pathognomonic feature is the discovery of the organism on microscopic section.

Almost any organ in the body may be affected. The meninges and lungs are the most commonly involved, but skin<sup>20</sup> and bone<sup>10, 21</sup> lesions occur in a small but significant percentage. Rarely, the eye<sup>22</sup> or kidney<sup>23</sup> is involved. *C. neoformans* has even been reported as the causative agent in a case of subacute endocarditis.<sup>24</sup> An association with a variety of other diseases, especially Hodgkin's and other malignant lymphomas, is common, but this is not so frequent as is supposed by most physicians.<sup>1, 10</sup> A number of cases with coexistent tuberculosis have been reported,<sup>3, 10</sup> but the association with sarcoidosis,<sup>25</sup> rheumatoid arthritis, and cancer of the breast<sup>1</sup> is probably on the basis of chance alone, or of generalized lowered resistance. Certainly, it is safe to say that at least 80% of cases of cryptococcosis are infections representing the primary disease of the affected patient.<sup>3, 5, 7, 9, 11-14</sup>

The epidemiology of the disease is incompletely understood. The organism has been cultured frequently from the soil, especially in association with pigeon droppings.<sup>1, 26, 27</sup> This relationship is apparently not due to the pigeons' harboring the organism, because attempts to isolate it from the gastrointestinal tracts of 20 young pigeons from nests with a high yield of fungi were unsuccessful.<sup>27</sup> As is the case with tuberculosis, it is probable that there is a variety of portals of entry. The most common is believed to be the lungs, the evidence for this being based on the frequent occurrence of long-quiescent pulmonary foci. Takos has shown that the gastrointestinal tract is a possible portal of entry. He fed large numbers of organisms to monkeys, and produced generalized disease without evidence of lesions

in the gastrointestinal tract. Thus, the failure to find clinical mucosal lesions does not eliminate the gastrointestinal tract as a portal of entry. The fact that the organisms have been found in milk and on peach skins supports this possibility.<sup>28</sup> The report of a number of cases of primary dermatologic cryptococcosis with systemic involvement implicates the skin as an occasional portal of entry.<sup>20</sup>

The clinical manifestations of cryptococcosis are protean. Often there are none, and the disease is discovered quite by accident at the time of a routine chest film which reveals a coin lesion. In these instances it is likely that the primary symptomatology of the patient was overlooked and dismissed as a "chest cold," the "flu," or some other minor, short-term respiratory illness. Litmann et al. compare pulmonary cryptococcosis to coccidioidomycosis, of which it has been stated that one meningitis case emerges from every 2,000 clinical and subclinical pulmonary infections. Using this ratio, they postulate that there may be as many as from 5,000 to 15,000 clinical and subclinical cases of pulmonary cryptococcosis each year in New York City alone.<sup>26</sup> This may seem excessive, but, when looked for, small foci of cryptococci have frequently been found in the lungs of people dying from totally unrelated causes.<sup>1</sup> Respiratory symptoms, when they do occur, are nonspecific, and run the gamut from cough and hemoptysis through dyspnea and chest pain. Sputum is not characteristic, and is frequently scant.<sup>8</sup> Meningitis is seldom acute, and it more nearly resembles tuberculous meningitis than other forms of meningitis.<sup>2</sup> Although death usually results in a few months, there is a definite tendency to chronicity with exacerbations and remissions. Likewise, there is nothing characteristic in the renal, skeletal or skin lesions, so that the diagnosis must rest upon biopsy and culture.

The chest roentgenogram is important. In general, there are three different types of pulmonary disease as viewed by the roentgen-ray. Undoubtedly the most common is the "coin lesion," in which the tumor has a fuzzy border sharply demarcated from surrounding normal lung.<sup>29</sup> Cavitation is uncommon but has been reported.<sup>11, 12</sup> Calcification is extremely rare.<sup>7</sup> The second type simulates miliary tuberculosis, in that there are widely disseminated nodular lesions in a background of linear infiltrate. Finally, there is the infiltrative type, which may resemble viral pneumonia.<sup>29</sup> Radiologists generally stress that hilar adenopathy is unusual. This fact may assist in the differentiation of cryptococcosis from tuberculosis, coccidioidomycosis and sarcoidosis, in which hilar adenopathy is more frequent.<sup>3, 29</sup> Pleural effusion is mentioned as occurring rarely.<sup>29</sup>

The diagnosis rests upon recovery of the organism from the appropriate body fluid, or its demonstration on microscopic tissue section. Pathogenicity studies, carried out by injecting white mice, may be helpful but are not always reliable. Most of the nonpathogenic fungi do not grow at 37° C., so that positive cultures obtained at this temperature are likely to

be significant. Multiple positive cultures, especially from different body fluids, strongly suggest pathogenicity. These should not be ignored, no matter how bizarre the clinical picture.

Until recent years, treatment was unsatisfactory. Pulmonary granulomas and unresolved pneumonias could be surgically removed. However, although this often resulted in cure,<sup>5, 7, 10-14, 29</sup> there are reports of subsequent meningitis and death.<sup>3, 9, 22, 30</sup> The surgeon attacking this disease had no agent to prevent dissemination as a result of the operation. A variety of chemical and antibiotic agents was tried, with little success until the advent of amphotericin B. The drug is not easy to administer. It is best given intravenously.<sup>1, 8</sup> There are many annoying side-reactions, the most common of which are nausea, vomiting, chills and fever. Elevations of the blood urea nitrogen have been reported, and recurrent thrombophlebitis may plague both the patient and the physician.<sup>1, 8, 31</sup> Winn,<sup>31</sup> in describing the efficacy of the drug in coccidioidomycosis, makes some valuable comments on its administration. To prevent thrombophlebitis, he recommends using small gauge needles (e.g., #23), and starting in veins as peripheral as possible. Periodic flushing of the infusion tubing with 5% glucose and water attached through a side arm, and the addition of 15 to 20 mg. of heparin, proved beneficial. Our first case had extreme difficulty with thrombophlebitis at the site of infusion, which did not respond to either heparin or Dicumarol. Hourly injections of 1 c.c. of 1% solution of procaine through the tubing solved the problem. Chills and fever were controlled by premedication with aspirin and antihistaminics. Nausea and vomiting were controlled by slowing the infusion. Rises in the blood urea nitrogen responded to the temporary lowering of dosage. Although the manufacturer recommends using the drug on alternate days, Winn reported little difficulty using full dosages of 1 mg./Kg. daily for long periods of time.<sup>31</sup>

It now seems likely that cryptococcosis in all its various forms will be amenable to both medical and surgical management, and that a combined approach to lesions requiring surgery will help to prevent recrudescences in patients with apparently localized bony or pulmonary disease. Only a period of many years of observation will provide the answer to the question of whether amphotericin B alone is satisfactory treatment for cryptococcus pneumonia. For the present, it would seem wise to follow the successful control of the acute pulmonary form with surgical removal of the affected segments of lung. This was strongly recommended to two of the patients herein reported, but was refused.

#### CONCLUSIONS

The discovery of three cases of pulmonary cryptococcosis, occurring during a period of three years in a 300-bed naval hospital, supports the contention of the literature that this entity is not rare, and should be con-



sidered in the differential diagnosis of "coin lesions," unresolved or slowly resolving pneumonia, and pulmonary infiltration of uncertain etiology. In the acute pneumonic form, the diagnosis can be made by sputum culture. The growth of *C. neoformans* at 37° C. on repeated cultures should not be ignored or ascribed to contamination.

Cryptococcus pneumonia may produce impressive primary pulmonary symptomatology. The lack of association of any of these cases with other significant disease is not an oddity, and illustrates that *C. neoformans* infection is usually an independent clinical entity.

Cryptococcal meningitis is usually preceded by pulmonary disease, which may be discovered by routine periodic chest x-ray. The natural history of cryptococcosis is another one of many good reasons why all coin lesions which are not known to have been stable over many years should be removed.

The gradually improving clinical and x-ray picture in the two cases receiving amphotericin B adds to the growing bulk of evidence that this agent is effective against *C. neoformans*. In our experience, side reactions associated with administration of this drug can be controlled. Periodic injections of 1% procaine through the infusion tubing were particularly successful in preventing thrombophlebitis in one of our cases.

The removal of residual foci of disease surgically, while continuing treatment with amphotericin B, appears advisable.

#### SUMMARY IN INTERLINGUA

Infectiones per *Cryptococcus neoformans* se recognosce de plus in plus frequentemente. Multe autores crede que le pulmones es usualmente le porta de entrata e que il es ab illac que se face le dissemination verso le meninges e altere organos. A causa del discoperta de amphotericina B e del facto que iste agente es efficace in le tractamento de infectiones per *C. neoformans*, le recognition del condition durante su precoce stadio pulmonar ha devenite importante.

Es presentate tres casos de cryptococcosis pulmonar. Duo del tres patientes se presentava a causa de pneumonia e esseva tractate a bon successo con longe cursos de amphotericina B per via intravenose. Le tertie esseva hospitalisate con meningitis cryptococcal a un tempore quando le roentgenogramma thoracic revelava un solitari lesion-massa. Iste patiente non recipeva amphotericina B. Post alicun tempore ille moriva. Le necropsia demonstrava que le lesion thoracic esseva un area de pneumonitis cryptococcal.

Es frequentemente considerate que cryptococcosis es inicialmente associate con altere statos pathologic, particularmente lymphomas maligne—que reduce le resistentia del patiente. Ben que iste conception es correcte in certe casos, al minus 80 pro cento del incidentia de cryptococcosis occurre sin altere morbos complicatori.

Le epidemiologia de cryptococcosis ha essite le thema de extense studios, sed illo remane pauco clar. Le organismo ha frequentemente essite retrovate in feces de columba e in specimenes de terra. Le infection pote acquirir se per inhalation, ingestion, o contamination de un vulnere cutanee (ben que isto ha non essite demonstrate definitivamente).

Le manifestationes clinic non es characteristic, e frequentemente il ha nulle tales usque al resultation de meningitis. Le phase pulmonar es associate con tres differente imagines roentgenographic: Le lesion in forma de pecia de moneta que es simile a

carcinoma o le infiltrato miliari que es simile a tuberculose miliari o le infiltrato que es simile a pneumonia viral. Le diagnose pote esser effectuate solmente super le base de culturation o biopsia. Le organismo cresce facilmente in varie terrenos a 37 C. Quando un cultura ab un date specimen revela le presentia de *C. neoformans*, infection clinic per ille agente debe esser considerate como un forte possibilitate in le patiente ab qui le specimen proveniva.

Le tractamento con amphotericina B per via intravenose es frequentemente successose, mesmo post que meningitis se ha disveloppate. Nausea, vomito, alior, febre, thrombophlebitis al sito del infusion, e azotemia transitori es frequente complicationes del therapia, sed usualmente illos pote esser reprimite de maniera que le interruption del tractamento non deveni necessari. Ben que anticoagulantes es possibilmente de valor in le manipulation del thrombophlebitis, iste forma de tractamento non resulta invariabilmente in le desirate successo. In casos de successo negative nos ha trovate altemente benefic le injection periodic de 1% de procaina in le tubo de infusion. Ben que in le hic presentate casos nulle intervention chirurgic esseva effectuate, nos crede que le ablation operatori de residue focos pulmonar post le restablimento ab le infection pulmonar es indicate, con continuation del tractamento a amphotericina B durante le phase chirurgic.

#### BIBLIOGRAPHY

1. McCullough, N. B., Louria, D. B., Hilbish, T. F., Thomas, L. B., and Emmons, C.: Cryptococcosis: Clinical Staff Conference at the National Institutes of Health, Ann. Int. Med. **49**: 642, 1958.
2. Fitzpatrick, M. J., Rubin, H., and Poser, C. M.: The treatment of cryptococcal meningitis with amphotericin B, a new fungicidal agent, Ann. Int. Med. **49**: 249, 1958.
3. Wolfe, J. N., and Jacobson, G.: X-ray manifestations of torulosis, Am. J. Roentgenol. **79**: 216, 1958.
4. Donnan, M. G.: Torulosis, J. Fac. Radiologists **10**: 17, 1959.
5. Jacobs, L. G.: Pulmonary torulosis, Radiology **71**: 398, 1958.
6. Anderson, K., and Beech, M.: Serological tests for early diagnosis of cryptococcal infection, M. J. Australia **2**: 601, 1958.
7. Kuykendall, S. J., Eldir, F. H., Jr., Weed, L. A., and Donoghue, F. E.: Pulmonary cryptococcosis, New England J. Med. **257**: 1009, 1957.
8. Lehan, P. H., Yates, J. L., Braskes, C. A., Larsh, H. W., and Furcolow, M. L.: Experiences with therapy of 60 cases of deep mycotic infections, Dis. of Chest **32**: 597, 1957.
9. McConchie, I. H., and Hayward, J. I.: *Torula histolytica*, *Cryptococcus neoformans*, granuloma of the lung treated by pulmonary resection, Post-Grad. M. J. **34**: 190, 1958.
10. Nichols, D. R., and Martin, W. J.: Cryptococcosis: clinical features and differential diagnosis, Ann. Int. Med. **43**: 767, 1955.
11. Webb, W. R., and Biggs, R. H.: Pulmonary cryptococcosis, Dis. of Chest **30**: 659, 1956.
12. Cornish, A. L., Balows, A., Chipps, H. D., and Holloway, J. B., Jr.: Isolated pulmonary cryptococcosis, Arch. Int. Med. **99**: 285, 1957.
13. Finney, C. T.: Solitary circumscribed lesion of the lung due to *Cryptococcus neoformans*, Am. Rev. Tuberc. **74**: 441, 1956.
14. White, M., and Arany, L. S.: Resection in pulmonary cryptococcosis (torulosis), J. Thoracic Surg. **35**: 402, 1958.
15. Louria, D. B., Feder, N., and Emmons, C. W.: Amphotericin B in experimental histoplasmosis and cryptococcosis, in Antibiotics Annual, edited by Welch, H., and Marti-Ibanez, F., 1957, Medical Encyclopedia, Inc., New York, p. 870.
16. Gantz, J. A., Nuetzel, A., and Keller, L. B.: Cryptococcal meningitis treated with amphotericin B, Arch. Int. Med. **102**: 795, 1958.

17. Editorials and Comments: Amphotericin B: treatment of cryptococcosis, *Canad. M. A. J.* **80**: 127, 1959.
18. Wilson, J. W.: Cryptococcosis: torulosis, European blastomycosis, Burs-Buschle's disease, *J. Chron. Dis.* **5**: 455, 1957.
19. Saliger, H. P.: Use of a urease test for screening and identification of cryptococci, *J. Bact.* **72**: 127, 1956.
20. Moore, M.: Cryptococcosis with cutaneous manifestations: four cases with a review of published reports, *J. Invest. Dermat.* **28**: 159, 1957.
21. Gosling, H. R., and Gilmer, W. S., Jr.: Skeletal cryptococcosis (torulosis): report of a case and review of literature, *J. Bone and Joint Surg.* **38A**: 660, 1956.
22. Fortune, C., Donnan, G., Colebatch, J., and Lubbe, T.: Torulosis, *M. J. Australia* **2**: 199, 1955.
23. Spivack, A. P., Nadel, J. A., and Eisenberg, G. M.: *Cryptococcus* renal infection: report of a case, *Ann. Int. Med.* **47**: 990, 1957.
24. Lombardo, T. A., Radson, A. S., and Dodge, H. T.: Mycotic endocarditis: report of a case due to *C. neoformans*, *Am. J. Med.* **22**: 664, 1957.
25. Heller, S., McLean, R. A., Campbell, C. G., and Jones, I. H.: A case of coexistent nonmeningitic cryptococcosis and Boeck's sarcoid, *Am. J. Med.* **22**: 986, 1957.
26. Litmann, M. L., and Schneierson, S. S.: *Cryptococcus neoformans* in pigeon excreta in New York City, *Am. J. Hyg.* **69**: 49, 1959.
27. Emmons, C. W.: Saprophytic sources of *Cryptococcus neoformans* associated with the pigeon, *Am. J. Hyg.* **62**: 227, 1955.
28. Takos, M. J.: Experimental cryptococcosis produced by injection of virulent organisms, *New England J. Med.* **254**: 598, 1956.
29. Bommati, J., Rogers, J. V., Jr., and Hopkins, W. A.: Pulmonary cryptococcosis, *Radiology* **66**: 188, 1956.
30. Palmrose, E. C., and Losli, E. J.: Cryptococcal meningitis: report of two cases, *Northwest Med.* **51**: 121, 1952.
31. Winn, W. A.: The use of amphotericin B in the treatment of coccidioidal disease, *Am. J. Med.* **27**: 617, 1959.

## THE CLINICAL SIGNIFICANCE OF CIRCULATING PANCREATIC ANTIBODIES \* †

By M. J. MURRAY, M.D., M.R.C.P., and A. P. THAL, ‡ M.D.,  
Minneapolis, Minnesota

THE discovery of circulating antibodies to thyroid tissue and thyroglobulin<sup>1</sup> led us to believe that iso-antibodies to pancreas might be present in chronic pancreatitis. Experimental studies, which included the production of chronic pancreatitis in animals and sensitization of animals to injected pancreatic extracts, clearly showed that antibodies to isologous pancreas were present in the sera of these animals.<sup>2</sup> We were then able to show in a preliminary study that the sera of patients with chronic pancreatic disease and carcinoma of the pancreas contained iso-antibodies specific to human pancreas.<sup>2</sup> Auto-antibodies to human pancreas have also been detected.<sup>3</sup> The present study is concerned with the clinical significance of iso- and auto-antibodies to human pancreas.

### MATERIALS AND METHODS

*The Preparation of Antigen:* Antigen was freshly prepared from human pancreas obtained either at operation or at autopsy. Where possible, blood was flushed out of the vessels by perfusion with saline. The surrounding fat and vessels were trimmed off. Ten grams of pancreas in 100 ml. of distilled water were homogenized in a Waring blender for 90 seconds and then filtered through gauze. The filtrate was centrifuged at 10,000 r.p.m. for 30 minutes. The middle layer of the three which separated was frozen in small aliquots to be used as antigen. Originally, pooled human pancreas was used, but now only the most reactive individual pancreas is used.

*The Hemagglutination Technic:* The technic described by Boyden<sup>4</sup> was used, and the tanned red cells were exposed to 1/100 dilution of the antigen.

*The Gel-Diffusion Technic:* The technic of Ouchterlony was used.<sup>5</sup> The antigen was undiluted pancreatic extract, and was run against the undiluted serum gamma globulin of the patient. The Petri dishes were incubated at 37° C. for 36 hours and then placed at room temperature in a humidified atmosphere. They were read at two and four days.

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From the Department of Medicine and the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

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‡ Established Investigator, American Heart Association.

Requests for reprints should be addressed to M. J. Murray, M.D., Assistant Professor of Medicine, University of Minnesota School of Medicine, Minneapolis, Minnesota.

*Preparation of Serum Gamma Globulin:* Serum gamma globulins were extracted in 1.64 molar ammonium sulfate for 60 minutes at 10° C. The tubes were then centrifuged at 2,600 r.p.m. for 10 minutes and the precipitate was resuspended in borate-saline at pH 8.2. Gamma globulins were freshly prepared for each test.

*Production of Pancreatitis in Animals:* Chronic pancreatitis was produced in animals by injecting staphylococcal alpha exotoxin into the pancreas according to the method of Thal and Molestina.<sup>6</sup> Species and organ-specific antibodies appeared within two to four weeks.

*Production of Pancreatic Iso-antibodies:* Pancreatic homogenate suspended in Freund's adjuvant was injected parenterally into animals at weekly intervals according to the method of Thal et al.<sup>2</sup> Antibodies again appeared in two to four weeks. If these injections are continued for prolonged periods (nine or more months), there is evidence to suggest that chronic pancreatitis will develop.

TABLE 1

Condition	No. of Cases	Positive Tests
1. Proved chronic pancreatitis	32	30
2. Proved carcinoma of the pancreas	11	9
3. Cystic fibrosis of the pancreas	7	6
Total (proved)	50	45
1. Suspected but unproved chronic pancreatitis	6	6
2. Suspected but unproved carcinoma of the pancreas	4	4
Total (unproved)	10	10

#### THE CLINICAL STUDY

The clinical study developed naturally into two stages. In the first, the sera of patients with known chronic pancreatic disease were examined for the presence of circulating specific antibodies to an antigen prepared from human pancreas; the latter were obtained from autopsy or surgical material. Sera from selected and unselected controls were studied at the same time. In the second stage, when we were satisfied that specific antibodies to pancreas did exist, the sera of patients suspected clinically of pancreatic disease were examined as an aid to diagnosis. In general, the method of study was to examine the test serum or separated gamma globulin with the Boyden hemagglutination reaction or the gel diffusion technic, using either pooled or individual human pancreas as the antigen. The unknown serum and a normal serum were routinely run against pancreas and against liver, spleen and kidney antigens as controls.

It was clear that all of the healthy control sera from blood donors were nonreactors. A group of 228 sera from unselected hospital patients showed 10 positive reactions (to be discussed later). The results in pancreatic disease are recorded in table 1. From 32 cases of chronic pancreatitis, proved either before or after the study of the particular serum, 30 sera

showed a positive reaction, either by the precipitin test in the original study, or by the hemagglutination and gel diffusion methods. Two sera were persistently negative, one from a mild case of pancreatitis, the other from the well advanced stage of the disease. We have no satisfactory explanation for these negative results. We were able to test the sera of four patients against their own pancreas obtained at surgery. Three were negative. One patient, "K," with very active disease, was found to have serum gamma globulin which reacted strongly with his own pancreas. It was noticeable also that his pancreas was an extremely potent source of antigen for other reactions. This case has been described in detail.<sup>3</sup> The finding of true auto-antibodies in this case raised the interesting possibility that his disease was either precipitated by or aggravated by an auto-immunizing mechanism. Recent experimental work with animals in our laboratory supports this possibility. In all of the other cases we had assumed that the iso-antibodies were probably the result of pancreatic damage, and that they played little or no part in the production of the disease.

TABLE 2

Pancreatic Carcinoma	No. of Cases	Positive Tests
1. Carcinoma of the head	5	4
2. Carcinoma of the body	6	5
3. Lymphoma in pancreas	1	1
4. Carcinoma of ampulla	2	1
5. Carcinoma of bile duct	1	0
Total	15	11
1. Fibrosarcoma involving pancreas (3 months after pancreatectomy only)	1	0
2. Carcinoma of ampulla (3 years after pancreatectomy only)	1	0

After a prolonged spontaneous remission or successful surgical treatment, e.g., relief of ductal obstruction, the antibody titer fell and occasionally disappeared. With recurrences, however, it rose again.

Our experience with carcinoma of the pancreas was less extensive: it consisted of 11 cases, analyzed in table 2. Two were persistently negative. We have not been able to examine the pancreas thoroughly in all cases, but we suspect that a positive test in carcinoma may depend upon the presence of associated pancreatitis and/or ductal obstruction. We noted the presence of microscopic pancreatitis in a patient with a carcinoma of the ampulla who was a positive reactor, supporting the above contention. On the other hand, a case presenting clinically as carcinoma of the head of the pancreas with a negative test was found to be carcinoma of the bile duct, without involvement of the pancreas. It was interesting to note negative tests after two Whipple procedures, one three years earlier, for an ampullary carcinoma, the other three months earlier, for a fibrosarcoma invading the pancreas. Preoperative sera were not available in these two cases.

In our original report, a positive reaction was recorded in a case of cystic



TABLE 3

Controls	No. of Cases	Positive Tests
1. Blood donors	50	0
2. Unselected hospital patients	228	10
3. Selected controls	85	11
a. Diabetes mellitus	61	7
b. Abdominal carcinomatosis	12	3
c. Disseminated lupus erythematosus	3	1
d. Hypergammaglobulinemia	3	0
e. Rheumatoid arthritis*	6	0
Total	363	21

\* Cases with positive latex fixation.

fibrosis of the pancreas. We have now examined sera from seven patients with well developed disease, of whom six showed positive reactions. The antibody present in these cases does not always appear to be identical with that seen in adult pancreatitis when adult pancreas is used as the antigen. In some cases, if both the cystic fibrosis serum and the adult pancreatitis serum are placed in wells on a gel diffusion plate against a central well of adult pancreatic antigen, the developing bands are not confluent and do not form a classic chevron. All of the remaining 10 patients in table 1 have been strongly suspected of chronic pancreatic disease. The four with possible carcinoma of the pancreas have evidence of metastatic disease from an unidentified primary source. No follow-up on these patients is yet available.

#### CONTROLS

There were 228 unselected controls. These sera were obtained as unknowns from hospital patients. There were 10 positive reactors, all listed in table 4. Some of these sera (cases 1, 2, 6 and 7) reacted with other antigens, indicating a nonspecific antibody. In some (cases 8, 9 and 10), the possibility of pancreatitis could not be clearly excluded. Unfortunately, where there had been an operation (cases 3, 4 and 11), no reference to the pancreas had been made in the operation record.

Antibodies to colon and other tissues have been detected in the sera of patients with ulcerative colitis.<sup>7</sup> Thus, the positive reaction in case 3 (with ulcerative colitis) may have been a nonspecific reaction; on the other hand,

TABLE 4

#### Diagnoses Established in Positive Unselected Controls

1. Disseminated lupus erythematosus
2. Chronic glomerulonephritis
3. Chronic ulcerative colitis
4. Chronic cholecystitis
5. Diabetes mellitus
6. Nonbacterial endocarditis
7. Polyarteritis nodosa
8. Cholangiolitic hepatitis and Sjögren's disease
9. Alcoholic cirrhosis
10. Pulmonary emboli
11. Duodenal ulcer

pancreatitis was not clearly excluded. In the nonbacterial endocarditis (case 6) there had been infarction of many organs, resulting in tissue injury over a long period of time and probably in the production of antibodies to many organs. In the cholangiolitic hepatitis (case 8) there was a history of abdominal pain and diarrhea, so that pancreatitis could not be excluded. Carcinoma of the pancreas was suspected in a patient with pulmonary

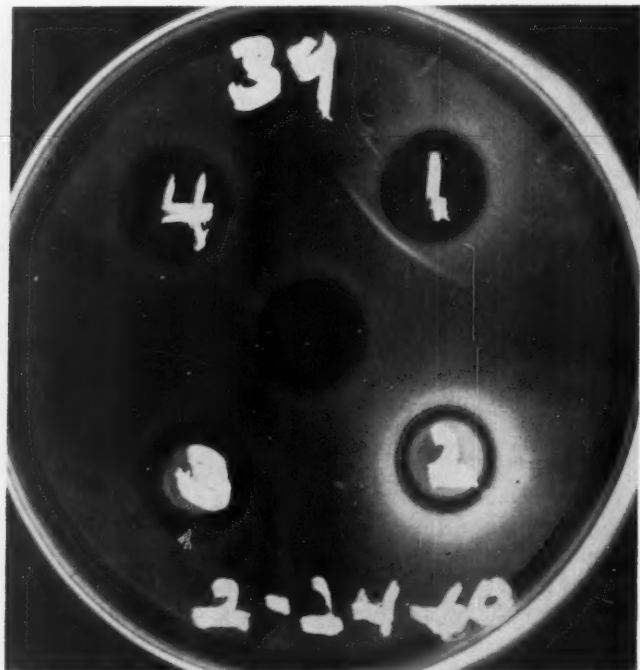


FIG. 1. Gel diffusion plate with serum from a case of chronic pancreatitis in the central well. Wells 1, 2, 3 and 4 contain antigens of pancreas, liver, kidney and spleen. A reaction has occurred only between the pancreatic antigen and the serum.

emboli (case 10), but no follow-up was available. There were three diabetics in this series who were negative reactors, but because of the one positive case, a further study of diabetics was undertaken.

The sera of 61 unselected diabetics have been examined. There were seven positive reactors, some markedly positive. Their histories were then reviewed, but nothing to suggest pancreatitis as a cause of diabetes could be found. They had all, however, received insulin for more than one year. There appear to be a number of possible reasons for these positive reactions: (1) The method is sufficiently sensitive to detect the moderate degrees of pancreatic damage frequently present in patients with diabetes mellitus.

Moderate degrees of pancreatic damage may easily be missed during gross examination at autopsy. The pancreatitis found with carcinoma of the ampulla of Vater is an example of the microscopic changes which can be seen in the absence of any gross change. (2) There is sufficient insulin in the antigen to detect insulin antibodies developing in response to injected insulin. (3) Impurities of pancreatic origin in the insulin may stimulate antibody production. Lapresle and Grabar<sup>8</sup> have shown such antibodies

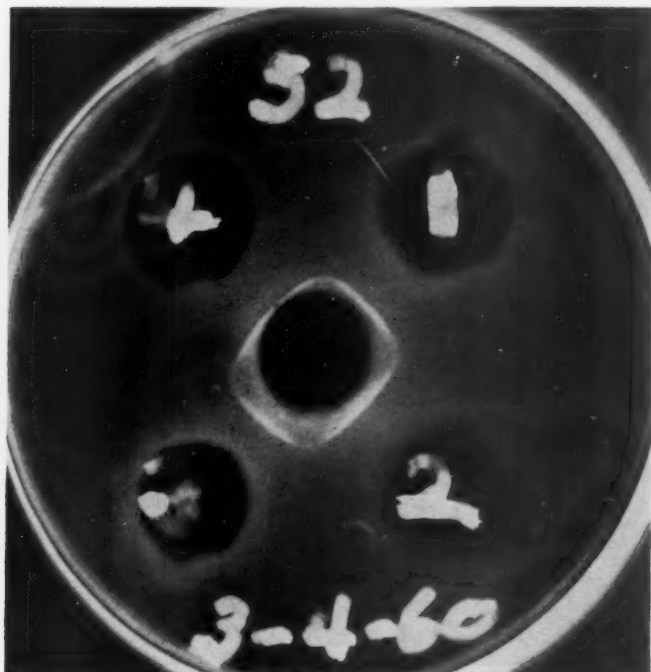


FIG. 2. Gel diffusion plate with pancreatic antigen in the central well. Wells 1, 2, 3 and 4 contain sera from patients with pancreatitis and carcinoma of the pancreas. All of the developing lines are confluent, indicating the identical nature of the antibodies.

in the sera of diabetics treated with insulin.<sup>4</sup> The antibodies occurring in response to impurities in the insulin may be damaging the pancreas and leading to further antibody production.

When the serum of a patient with chronic pancreatitis without diabetes and the serum of one of the seven positive diabetics are placed in wells on a gel diffusion plate against pancreatic antigens, they form a confluent chevron, indicating the identical nature of the antibodies. Further studies are still in progress on this problem.

Because of widespread organ damage in intra-abdominal carcinomatosis,

and the possibility of false-positive tests, 12 unknown cases were studied. No known pancreatic primary carcinomas were missed, but there were three positive tests in patients in whom the primary carcinoma remained undetected in spite of extensive clinical examination. Finally, a number of disease states with hypergammaglobulinemia were selected. All showed negative reactions, except for one case of disseminated lupus erythematosus. Six cases of rheumatoid arthritis with positive latex fixation test were negative.

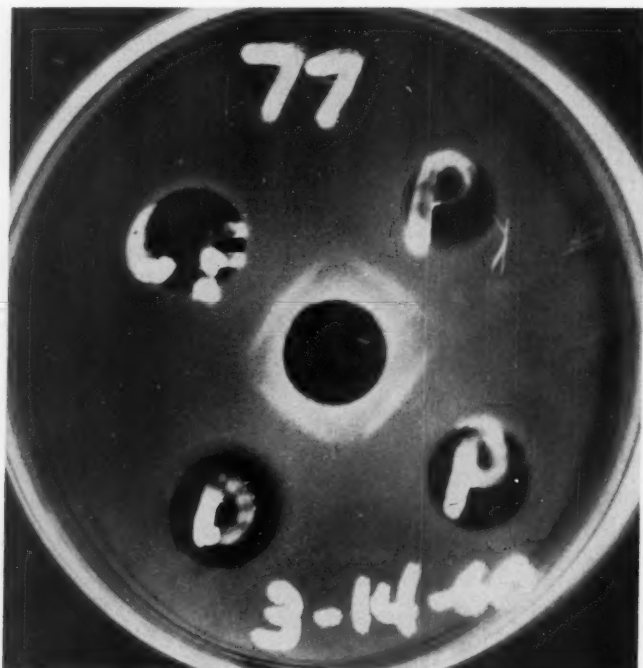


FIG. 3. Gel diffusion plate with pancreatic antigen in the central well. The surrounding wells contain sera from pancreatitis (P), diabetes mellitus (D), and cystic fibrosis of the pancreas (CF). The developing lines are confluent.

#### SUMMARY AND CONCLUSIONS

The majority of sera from patients with chronic pancreatic disease or carcinoma of the pancreas contain circulating antibodies specific to human pancreas. All of the control normal sera studied showed no reaction. However, the control sera from other disease states, in particular from diabetes mellitus, showed some positive reactions, which have been discussed.

Circulating antibodies to human pancreas in the absence of antibodies to other tissues suggest the possibility of chronic pancreatic disease or carcinoma of the pancreas. Although such antibodies are mostly iso-anti-

bodies, true auto-antibodies have been shown to occur. Experimental work in progress suggests that auto-immunization of animals with their own pancreas may lead to chronic pancreatitis after a prolonged period of time.

#### SUMMARY IN INTERLINGUA

Iso-anticorpo anti pancreas human esseva cercate in le seros de patientes con chronic morbo pancreatic. Seros de normales e de patientes non-pancreatic serviva de controlo. Quando extractos aquose de pancreas human es placiato como antigeno contra le seros sub investigation per medio del technicas de diffusion in gel de Ouchterlony e de hemagglutination de Boyden, reactiones positive es obtenite in chronic morbo pancreatic e certe altere statos pathologic. Normal seros de controlo esseva negative sin exception, sed plure casos de reaction positive esseva incontrate in morbos como disseminate lupus erythematosus, polyarthritus nodosa, colitis ulcerative, e diabete mellite. Reactiones positive contra antigenos additional es usual in iste nonspecific gruppo. Un modeste numero de positivitates (septe ex 61) esseva trovate in seros ab patientes con diabete mellite e sin signos clinic de pancreatitis chronic.

Le reaction esseva positive in 30 ex 32 casos demonstrate de pancreatitis chronic. In un de iste patientes, auto-anticorpo esseva detegite in le sero in tests con le pancreas de ille mesme que habeva essite obtenite al operation. Novem reactiones positive esseva obtenite in le seros de 11 patientes con carcinoma del pancreas e sex in le seros de septe patientes con cystic fibrosis del pancreas. Super le base de nostre studios il pare probabile que le iso-anticorpo anti pancreas human es le producto e non le causa del reaction inflammatori in le pancreas. Le detection de iso-anticorpo pancreatic va possiblementemente esser utile in confirmar le presentia de chronic morbo pancreatic.

#### BIBLIOGRAPHY

1. Doniach, D., and Roitt, I. M.: Auto-immunity in Hashimoto's disease and its implications, *J. Clin. Endocrinol. and Metabolism* **17**: 1293-1304, 1957.
2. Thal, A. P., Murray, M. J., and Egner, W.: Isoantibody formation in chronic pancreatic disease, *Lancet* **1**: 1128-1129, 1959.
3. Thal, A. P., Egner, W., and Murray, M. J.: Circulating antibodies in chronic pancreatic disease, *Surgical Forum* **10**: 240-243, 1959.
4. Boyden, S. V.: The adsorption of proteins on erythrocytes treated with tannic acid and subsequent hemagglutination by antiprotein sera, *J. Exper. Med.* **93**: 107-120, 1951.
5. Ouchterlony, O.: Antigen-antibody reactions in gels. IV. Types of reactions in co-ordinated systems of diffusion, *Acta path. et microbiol. scandinav.* **32**: 231-240, 1953.
6. Thal, A. P., and Molestina, J. E.: Studies on pancreatitis, *Arch. Path.* **60**: 212-220, 1955.
7. Broberger, O., and Perlman, P.: Auto-antibodies in human ulcerative colitis, *J. Exper. Med.* **110**: 657-671, 1960.
8. Lapresle, C., and Grabar, P.: Étude comparative de la benzidine bi-diazotée et de l'acide tannique dans les réactions d'hémagglutination obtenues avec des préparations d'insuline et des sérums diabétiques traités par l'insuline, *Revue franç. étud. clin. et biol.* **3**: 57-59, 1958.

# CLINICAL PATHOLOGICAL CONFERENCE

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## RECURRENT PULMONARY DISEASE IN A CHILD: CLINICAL PATHOLOGICAL CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH \*

*Moderator:* VERNON KNIGHT, M.D. *Discussants:* THEODORE L. BADGER, M.D.,  
Boston, Massachusetts; EMIL SCHULZ, M.D., and R. GERALD SUSKIND, M.D.,  
Bethesda, Maryland

### CASE REPORT

This 10½ year old male was admitted to the Clinical Center for the first time on August 19, 1957, with a presumptive diagnosis of pulmonary sarcoidosis.

*Present Illness:* Between the ages of two and 10 years, the patient had recurrent respiratory infections and occasionally small amounts of hemoptysis. A diagnosis of recurrent bronchitis was made. He had intermittently received iron therapy for an iron deficiency anemia. Although he had experienced convulsions before the age of five years, there is no history of any since. However, when he was eight years old he was hospitalized for complaints of headaches and staggering gait. No diagnosis was made at that time.

The patient was smaller than other children his age, tired easily, and complained intermittently of abdominal pains. In April, 1957, *four months before admission*, he had an acute episode of fever, chest pain and cough. He was treated with penicillin, but continued to have a slight hacking cough. In July, 1957, *one month before admission*, an x-ray examination of the chest revealed nodular densities in both lung fields, for which he was admitted to another hospital. Studies there included: hemoglobin, 9.1 gm./100 ml.; leukocyte count, 8,000/mm.<sup>3</sup>; differential count, normal. Urinalysis was normal. Skin tests for tuberculosis and fungal diseases were negative. Cultures of sputa, gastric and bronchoscopy washings were negative for tuberculosis. Cold agglutinin titer was 1:80. No gross abnormalities were recognized during bronchoscopy. After bronchoscopy the patient became acutely ill, with high fever, extreme dyspnea and cyanosis. He was treated with oxygen, intravenous prednisone, penicillin and streptomycin, and digitalis because of a questionably enlarged heart. Gradual improvement followed. A scalene node was removed and was believed to be normal histologically, and cultures from it were negative. A tentative diagnosis of sarcoidosis was made, and he was referred to the National Institutes of Health for study.

The patient was discharged receiving 5 mg. prednisone daily.

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Requests for reprints should be addressed to Vernon Knight, M.D., National Institutes of Health, Bethesda 14, Maryland.



*Twenty-four hours before admission* here, and several days after discharge from the other hospital, the patient again became acutely ill, with fever, increased respiratory rate and cyanosis.

*Past History:* The child had made numerous visits to a farm where chickens were raised. Well water was consumed at the farm. Usually the patient was a city dweller.

*Physical Examination:* Temperature, 37.8° C.; pulse, 130; blood pressure, 110/58 mm. of Hg; respiration, 52.

The patient was a small, emaciated, acutely ill boy in severe respiratory distress. The skin was slightly pale, and peripheral cyanosis was evident. There was no venous distention. Respirations were labored, rapid and shallow. There was percussion flatness over the right lower chest and an inspiratory lag was noted on the same side. The hemidiaphragms were low and moved poorly. Harsh breath sounds, moist râles, and short respiratory and prolonged expiratory wheezes were heard diffusely throughout the chest. There was questionable clubbing of the digits. The liver was palpated 1 cm. below the right costal margin. The splenic tip was felt.

*Laboratory Data:* Hemoglobin, 10.9 gm./100 ml.; hematocrit, 36%; white blood count, 16,000/mm.<sup>3</sup>, with 91 polymorphonuclears, 7 lymphocytes and 2 eosinophils; sedimentation rate, 23 mm./min. (Westergren). Urinalysis was normal. C-reactive protein, 4 plus; blood urea nitrogen, 13; total cholesterol, 150; calcium, 10.2, and phosphorus, 4.8 mg./100 ml. Serum CO<sub>2</sub> content, 23; chlorine, 98 mEq./L.; sodium, 138 mEq./L.; potassium, 4.7 mEq./L.; alkaline phosphatase, 2.8 units; serum total protein, 6.3; albumin, 3.3; and globulin, 3 gm./100 ml. Thymol turbidity, 4; cephalin flocculation, 2 plus. Serum transaminase (SGOT), 60 units/ml.; several days later, 19 units/ml. Total bilirubin, 1.1; direct, 0.14 mg./100 ml. Urine urobilinogen, less than 0.1 Ehrlich unit. Gastric washings were negative for acid-fast bacilli on three occasions. Bone marrow was histologically normal, and cultures failed to yield bacteria (aerobes and anaerobes), fungi or tubercle bacilli. Cold agglutinin titers were elevated to 1:320 and 1:640. Direct and indirect Coombs' tests were negative. Throat cultures yielded *Pseudomonas* and *Klebsiella* organisms.

*Hospital Course:* Treatment was started with hydrocortisone intravenously, isoniazid, tetracycline and streptomycin. Over the first 36-hour period the respiratory rate rose progressively to 180, and the pulse rate to 190. Venous pressures remained normal. X-rays taken the second day showed extensive infiltration in both lungs. By the third day the patient was beginning to improve clinically, with marked improvement in respiratory function and lessening of cyanosis, although a pleural friction rub was heard constantly. Laboratory findings were unchanged except for a decrease in the cold agglutinin titer to 1:80. Repeated skin tests were negative, as were complement fixing tests for fungal diseases. Cortisone treatment was discontinued after eight days, but antituberculous therapy was continued for three weeks. Steady improvement occurred but, beginning on the eighteenth day, and for several days thereafter, the patient had small amounts of hemoptysis. By x-ray examination there was evidence of bilateral pulmonary infiltration, most marked in the right lower lobe. Papanicolaou smears of sputum revealed hemocytolytic cells but no neoplastic forms. Improvement continued thereafter. Hemoglobin determinations and white blood counts were within normal limits. X-rays of the chest, however, persistently showed a fine underlying reticulate pattern. Ambulation was increased and tolerated without respiratory difficulty or fever. The patient was doing school work. The patient was discharged to his home on October 26, 1957, with no orders for further medication.

The patient was re-admitted on November 4, 1957, because a roentgenogram of the chest showed recurrent, diffuse, patchy pneumonitis.

*Physical Examination:* Temperature, 38.2° C.; pulse, 92; respiration, 22. The

patient did not appear to be ill, although he was somewhat pale. The chest was clear to percussion. The configuration of the chest appeared to be normal. Both diaphragms moved well. A pleural friction rub was noted on the right side. Râles were not heard, but breath sounds were diminished in the right base. The findings were not constantly present.

*Laboratory Data:* Hematocrit, 38%; hemoglobin, 11.4 gm./100 ml.; white count, 9,000/mm.<sup>3</sup> Differential count showed 60 polymorphonuclears, 30 lymphocytes, 7 monocytes and 3 eosinophils. Sedimentation rate, 20 mm./hr. Urinalysis was normal. Serum iron, 22; iron binding capacity, 126; total iron binding capacity, 148 micrograms Fe/100 ml. LE cell preparation, C-reactive protein, cold agglutinins, and indirect and direct Coombs' tests were negative. Serum total protein, 6.5 gm./100 ml. Electrophoresis of serum proteins: 50% albumin, 5% alpha-1, 15% alpha-2, 16% beta, and 14% gamma globulin. Tuberculin, histoplasmin and blastomycin skin tests were negative. Osmotic fragilities of incubated and nonincubated red blood cells were normal. An electrocardiogram showed evidence of some right ventricular preponderance.

*Hospital Course:* Skin and muscle biopsies were normal histologically. An open right thoracotomy was performed and the tip of the lower lobe of the right lung was biopsied. Grossly the lung was heavier and more boggy than usual. (Microscopic findings are omitted for purposes of the conference.) Prior to this operation, the patient's vital capacity had been 700 c.c. (predicted, 3,200 c.c.), and maximal breathing capacity was 47.5 L. per minute (predicted, 79 L. per minute).

Forty-eight hours postoperatively the patient developed severe dyspnea, tachypnea, cyanosis and consolidation of the left lung. He was treated with oxygen and hydrocortisone, and after three days improved gradually. During this crisis the hematocrit fell from 37% to 30%; hemoglobin dropped from 12 gm./100 ml. to 9 gm./100 ml., and reticulocytes increased from 1.2% to 4.7%. The cold agglutinins rose to 1:640 against standard type O cells, and to 1:2560 against his own cells. Coombs' tests remained negative. The sedimentation rate and C-reactive protein became elevated, and there was a moderate leukocytosis with a shift to the left.

When the patient had no longer any evidence of pneumonitis, ventilation studies were repeated. Vital capacity and maximal breathing capacity were one-fourth and one-half of normal, respectively.

Later, after an interval of general improvement, the patient again had fever, cough and respiratory distress. Percussion dullness and inspiratory lag were demonstrated on the left side. There was x-ray evidence of bilateral infiltration. The concentration of hemoglobin decreased. At this time the patient was receiving 25 mg. hydrocortisone twice daily. Resumption of the higher dose of hydrocortisone caused prompt resolution of this process, and the patient was discharged December 23, 1957.

Approximately 12 hours prior to his third admission, on February 8, 1958, the patient complained of severe shortness of breath on exertion, and his pulse became very rapid.

*Physical Examination:* Temperature, 38° C.; pulse, 180; respiration, 40; blood pressure, 110/60 mm. of Hg. The lips and nail-beds were slightly cyanotic. Percussion dullness and inspiratory lag were noted on the right side. Râles and gurgling sounds were heard in the right lower lobe. The peripheral veins were not distended, and there was no hepatosplenomegaly.

*Laboratory Data:* Hemoglobin, 13.1 gm. 100 ml.; hematocrit, 41%; reticulocytes, 2%; white blood cell count, 16,600/mm.<sup>3</sup>, with 74 polymorphonuclears and 22 lymphocytes. Chest x-ray showed patchy infiltrates in both lung fields, more prominent in the right side.

*Hospital Course:* Oxygen and hydrocortisone were administered, and the patient appeared to improve slightly. About 12 hours after his admission he became cyanotic

while in an oxygen tent. The respiratory rate increased to 150, and shortly thereafter he became comatose. Two hours before death, the patient passed dark urine, negative for bile but strongly positive for occult blood. No fresh red cells or red cell casts were seen on microscopic examination. The patient died on February 10, 1958, on the second day of his third Clinical Center admission.

**DR. VERNON KNIGHT:** I am delighted to introduce Dr. Theodore L. Badger, Assistant Clinical Professor of Medicine at Harvard Medical School. He will discuss this case of a patient from the National Institute of Allergy and Infectious Diseases.

**DR. THEODORE L. BADGER:** In reviewing the case history, one finds a young man extraordinarily subject to recurrent pulmonary infections, occasionally accompanied by hemoptysis. Agammaglobulinemia seemed unlikely, since when he was 10 years of age, gammaglobulin values were actually high.<sup>1</sup> He was small for his age. Fibrocystic disease is another possibility, but is usually associated with a more characteristic history.<sup>2</sup> However, there are children in whom the disease may not involve the pancreas but does involve other exocrine glands, or may be entirely pulmonary in character, with no gastrointestinal symptoms or manifestations of pancreatic deficiency.

During the early months of 1957 the patient had a persistent cough and intermittent febrile episodes. In July, 1957, an x-ray examination of the chest was said to reveal nodular densities in both lung fields, and for that reason he was admitted to another hospital. Studies there demonstrated a mild anemia. Skin tests were negative. Sputum studies and gastric washings showed nothing of any importance. Cold agglutinins were weakly positive. Bronchoscopy was entirely normal. The patient was treated with oxygen, intravenous prednisone, penicillin and streptomycin. He was given digitalis because of a questionably enlarged heart and tachycardia. Improvement was slow. Scalene node biopsy was negative. In our hands this procedure has been a useful technic for identifying bizarre and obscure pulmonary lesions in which a diagnosis has not been made by other means. In about one-fourth of patients, one may obtain some diagnostic help from scalene node biopsy when everything else has failed; in sarcoidosis, for example, about 35% of scalene nodes show characteristic changes.

The patient was admitted to the Clinical Center for further study. Shortly before admission he became acutely ill, with fever and respiratory difficulties. The possibility of cryptococcosis,<sup>3</sup> histoplasmosis<sup>4</sup> or some of the other fungal infections must be considered in individuals with unusual or characteristic histories of exposure. In this particular case, these matters seem irrelevant.

Pulse and respiratory rates were rapid at the time the patient was admitted. A respiratory rate of 52 is considerably higher than we are accustomed to seeing in ordinary infections such as bacterial or viral pneumonia, even though they may be miliary or lobar in type. One begins to suspect, even at this point, that we are faced with a physiologic problem in which there is interference with the diffusion of oxygen across the alveolar membrane, because of alveolar-capillary block.<sup>5, 6</sup> The clinical picture this patient presented was one of respiratory effort to compensate for poor oxygenation of the blood. We do not have specific data concerning alveolar-capillary block.

On auscultation there were diffuse harsh breath sounds, with an inspiratory

short wheeze and a longer expiratory wheeze. I am not quite sure why the patient had these wheezes, but any acute process in the lung is prone to produce some bronchial spasm. The important thing was that the sounds were harsh and were very well heard. This indicates that he was moving alveolar air reasonably well and that there was no obstructive element, but there is not much to indicate pulmonary emphysema to explain poor oxygenation.

Laboratory data on this first admission to the Clinical Center showed a mild hypochromic anemia, as had been the case on the previous admission elsewhere. It is difficult to tell if this was a microcytic or normocytic variety, as the cell indices were not given.

The C-reactive protein was 4 plus but, like the sedimentation rate, was nonspecific. The 2-plus cephalin flocculation test suggested some degree of liver dysfunction, but the patient had had high fever. The serum transaminase was 60 units—slightly high—but it fell to 19 units a short time later, and would be indicative of transient liver dysfunction, or is at least consistent with it, in the absence of coronary artery disease. Other chemical tests and the bone marrow were essentially normal. Coombs' tests were negative.

I am a little intrigued by the elevated titer of cold agglutinins (1:640) because it is a very nebulous test, and if the globulins are elevated—in particular the macroglobulins—the cold agglutinins may be positive. They are sometimes positive in chronic hemolytic anemia, and occasionally in acute hemolytic anemias.

During this first admission the patient was critically ill and no diagnosis was made. Treatment was started with hydrocortisone intravenously, isoniazid, tetracycline and streptomycin. Under the circumstances, the antituberculous therapy was employed, probably because of the diagnostic uncertainties concerning the pulmonary lesion. However, since the tuberculin test was completely negative in all strengths, tuberculosis need not be considered too seriously in this young man. Most individuals infected with the tubercle bacillus show a positive tuberculin test, or react in some degree to the tuberculin test if they are in a state of good nutrition and are not giving in to a fatal disease.

Dr. Schulz, would you show the x-rays now?

DR. EMIL SCHULZ: Our first chest x-ray (figure 1) is similar in appearance to the previously discussed film, taken elsewhere six weeks earlier. The skeletal structures are small but otherwise normal in appearance. Liver and spleen are normal in size. The heart and great vessels appear to be normal. The mediastinum is lobulated and widened, and the hila are enlarged, indicating lymphadenopathy. Extensive infiltrates are present throughout both lungs. These are most marked in the perihilar regions, and fan out toward the periphery. The bronchi are contrasted by surrounding extensive consolidation.

DR. THEODORE L. BADGER: He was certainly a very narrow-chested young man.

DR. EMIL SCHULZ: That is right; he was a small, 10 year old child.

DR. THEODORE L. BADGER: Over the first 36 hours the patient's condition gradually deteriorated. Respiratory rates rose as high as 180—extraordinarily high, even for a child—and the pulse as high as 190. Venous pressures remained normal, however, and by the third hospital day the patient showed a rather dramatic improvement.

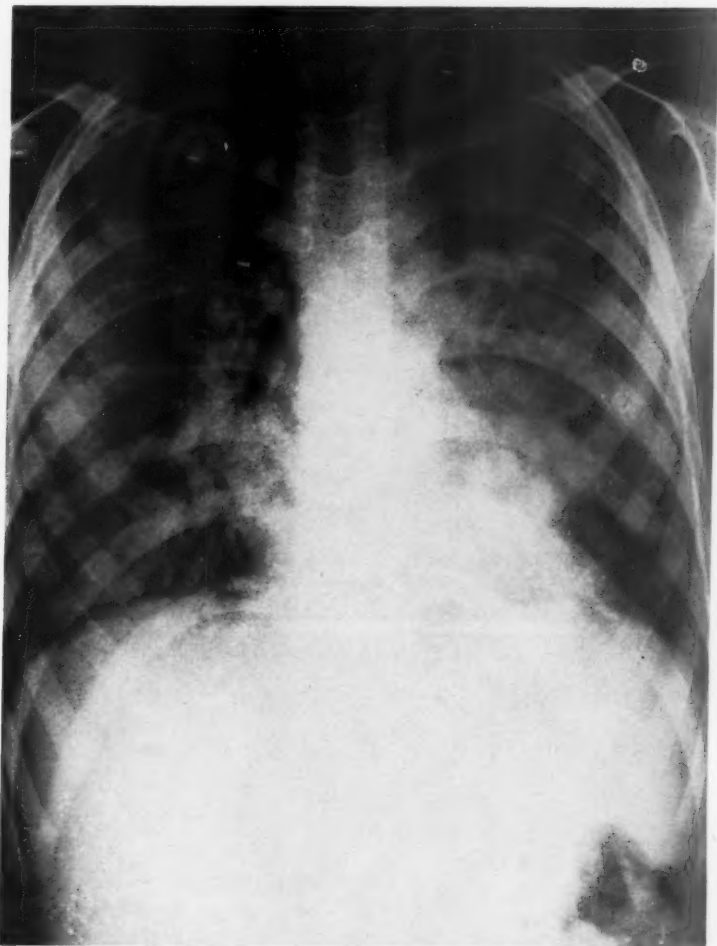


FIG. 1. The first admission chest x-ray shows hilar and mediastinal lymphadenopathy and extensive blotchy infiltrates throughout both lungs. Note the air bronchogram.

May we see the films taken the day after admission?

DR. EMIL SCHULZ: We observe clearing of the lungs but see persistence of hilar adenopathy. Minimal perihilar infiltration is evident. Films (figures 2A and 2B), taken some time later during this admission, showed sequential exacerbations and regression of pulmonary infiltrations. After each regression, residual reticular changes are noted.

DR. THEODORE L. BADGER: Do you consider these to be diffuse nodular lesions?

DR. EMIL SCHULZ: The residual changes are finer and reticular in character.

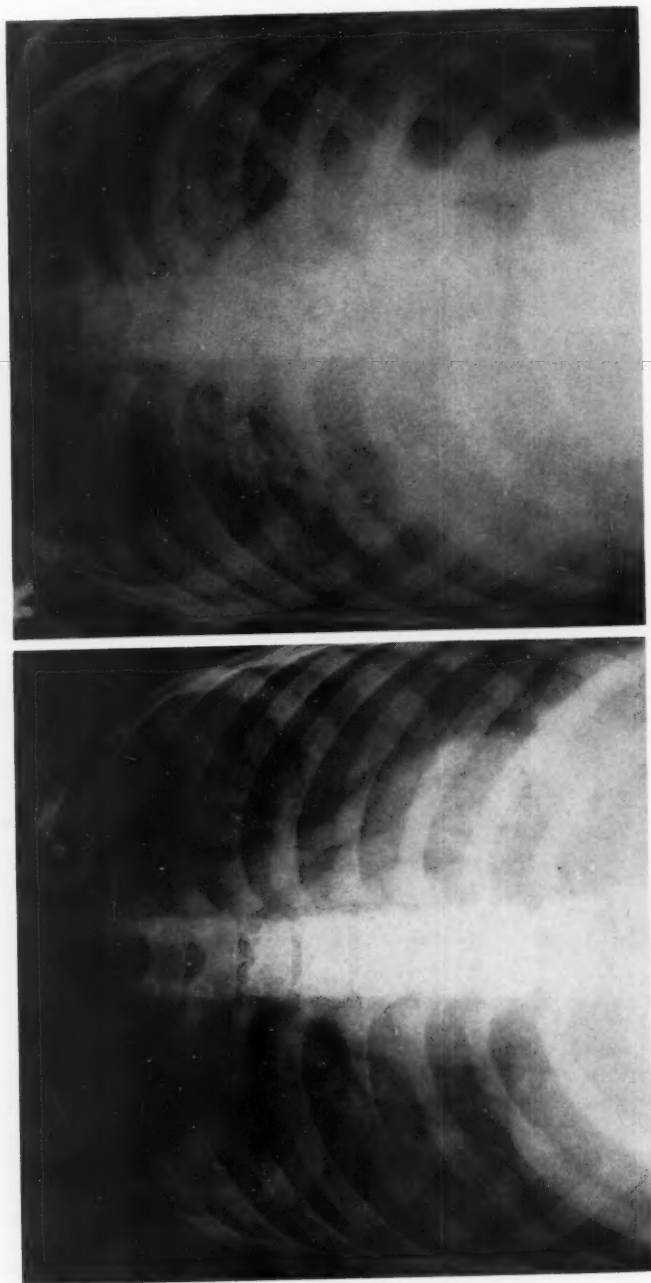


FIG. 2. *A* and *B*. Progression of pulmonary infiltration is noted three and five days after admission.



DR. THEODORE L. BADGER: I think that is important to remember.

DR. EMIL SCHULZ: Sinus films showed right antral and right ethmoidal clouding and partial opacification.

DR. THEODORE L. BADGER: I would like to draw attention to the rather rapid appearance of these changes. To me, the bilateral symmetry of the process is of some importance, as is the very delicate, fine ground-glass nodular type of shadow, which is lacelike and minute in its nodularity. Is that correct, Dr. Schulz?

DR. EMIL SCHULZ: During exacerbations, the infiltrates become fluffy, blotchy and extensive. Even when an air bronchogram is seen, the surrounding pulmonary tissue is not densely opacified. With each clearing of the process, we see more extensive residual fine fibrotic changes in the lungs. The heart size remains normal throughout the patient's hospitalization.

DR. THEODORE L. BADGER: Although the patient showed dramatic improvement while receiving corticosteroids, there was little change in the laboratory findings, except for the cold agglutinin titer, which dropped to 1:80 after reaching a high of 1:640. Skin tests for tuberculosis and histoplasmosis were again negative, as were complement fixation tests for histoplasmosis and blastomycosis. These tests were performed while corticosteroids were not being used.

Antituberculous and antibacterial therapy was continued, but cortisone was stopped. There was steady improvement, but on the eighteenth hospital day the patient began spitting up small amounts of dark red blood, and continued to do so for several days. Papanicolaou smears of the sputum revealed hemocytolytic cells but no neoplastic cells. At the same time there was an apparent spread of the pneumonitis in the right lower lobe.

DR. EMIL SCHULZ: The x-ray findings were similar in appearance to those we have shown and described previously.

DR. THEODORE L. BADGER: After this, the patient showed gradual, steady improvement. Hemoglobin and white blood cell counts became normal. His chest x-ray continued to show a fine underlying reticulate pattern, which I think should be remembered. By the time he was able to be discharged to his home he was ambulatory, afebrile and attending school.

On November 4 the patient was re-admitted because a roentgenogram of the chest showed recurrent, rather massive patchy pneumonitis. On this second admission he did not appear to be very ill. He had no rales or rhonchi in his chest, and breath sounds varied from being normal to somewhat diminished at the right base. It is important to note that he had good diaphragmatic motion, because this leads one away from all thoughts of obstructive emphysema.

Laboratory findings revealed little of interest. The hematocrit was 38%, and L.E. cell preparations were negative. The serum iron was 22, and the serum iron binding capacity, 126, somewhat reduced and consistent with a hypochromic anemia.

The cold agglutinins were negative. Coombs' tests were negative. I think the Coombs' test is quite valuable for demonstrating a hemolytic anemia, yet it is not always positive. The stool urobilinogen may be the only laboratory procedure which will be positive during hemolytic episodes.

The blood chemical studies were essentially normal. Electrophoretic pattern of serum proteins showed 50% albumin, 5% alpha-1, 15% alpha-2, 16% beta and

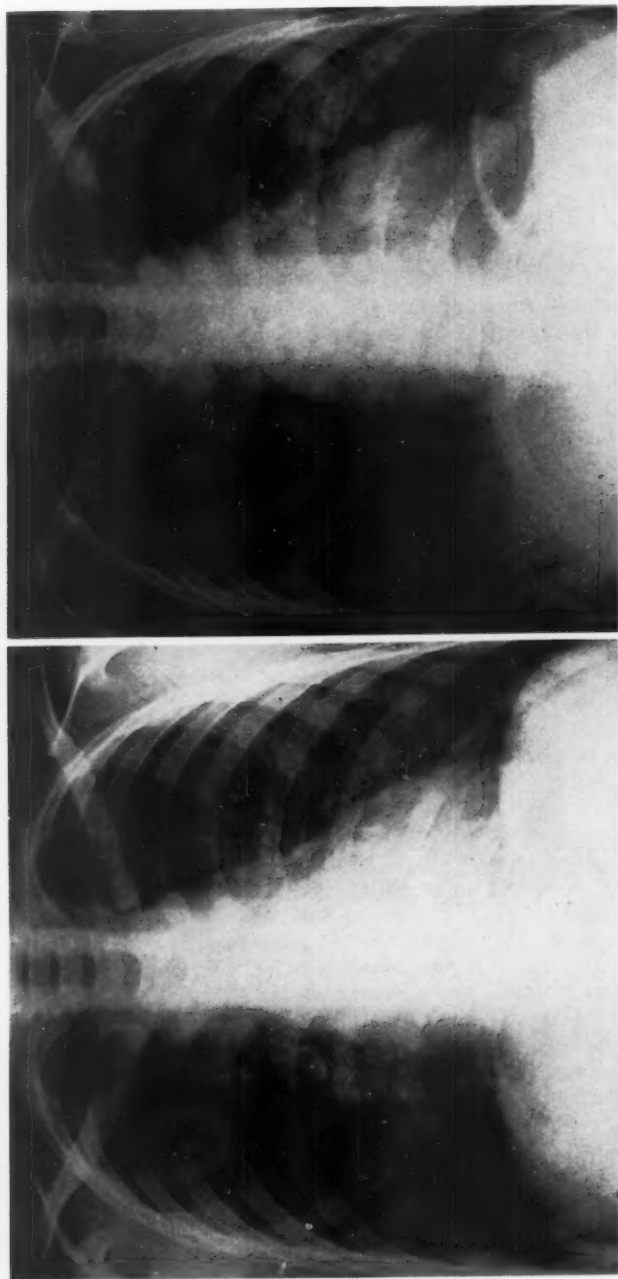


FIG. 3 (*left*). Discharge chest x-ray, two months after first admission, shows residual hilar and mediastinal adenopathy. Residual fine reticular pulmonary fibrosis is present.

FIG. 4 (*right*). Clinic visit chest x-ray, two weeks after discharge, again shows exacerbation of pulmonary infiltration.

14% gamma. Perhaps the gamma was a little low and the albumin slightly elevated. The electrocardiogram was normal.

Chest x-ray revealed a patchy pneumonitis, but it showed improvement since the previous examination.

DR. EMIL SCHULZ: X-rays taken at the end of the previous admission showed clearing of the perihilar infiltrates (figure 3). Residual adenopathy and reticular fibrotic changes are evident. The liver and spleen have not changed in size.

An x-ray taken after the patient's discharge shows recurrence of the diffuse infiltrative process (figure 4).

A skin biopsy revealed no abnormalities. Because the patient remained a diagnostic problem, it was decided to do an open thoracotomy and lung biopsy. His vital capacity prior to operation was only 700 c.c., with a predicted vital capacity of 3,200 c.c. His maximal breathing capacity was only 47.5 L., compared to a predicted 79 L. A vital capacity only one fourth of expected normal indicated an extraordinarily restrictive defect in this young man.<sup>7, 8, 9</sup> It would have been of interest at this point to have direct evidence for or against bronchial obstruction. The observation that the diaphragms moved well suggests there was no obstructive defect. There did exist, however, a significant diffusional defect in addition to the restrictive (fibrotic) changes. There was nothing particularly diagnostic in the gross observations at thoracotomy.

On the third day after surgery the patient developed signs of severe dyspnea, tachypnea and cyanosis. Examination revealed consolidation of the left lung.

May we see the x-rays?

DR. EMIL SCHULZ: Progressive extensive pulmonary infiltration and progressive mediastinal widening occurred over a period of a few days (figure 5).

DR. THEODORE L. BADGER: The patient was then treated with hydrocortisone, with marked improvement in his condition. However, the hematocrit fell from 37% to 30%, and the hemoglobin from 12 gm. to 9 gm. The reticulocytes increased from 1.2% to 4.7%, and the cold agglutinins, which had previously been negative, rose to 2,560 against his own cells. Coombs' test, both direct and indirect, remained negative, but the sedimentation rate became markedly elevated.

Putting this information together, we find indication of the development of an acute hemolytic anemia. Very often this means some degree of splenic involvement, like a case of acute hemolytic anemia associated with Boeck's sarcoid, reported in the *New England Journal of Medicine*.<sup>10</sup> Here, splenectomy was effective in alleviating the hemolytic anemia. The spleen showed some degree of involvement, with sarcoid granulomatous changes. In the present case, origin of the hemolytic anemia remains obscure. I think it might be informative at this time to see the cytologic study of the sputum.

DR. R. GERALD SUSKIND: If you are willing, Dr. Badger, we will just give you the opportunity to look at the slide.

DR. THEODORE L. BADGER: I think there are a number of macrophages, and that there are hemosiderin granules within the cytoplasm of the cells. A number of polymorphonuclears, some lymphocytes and some monocytes are also present. I see no microorganisms, although I am not sure this specimen was stained for organisms.

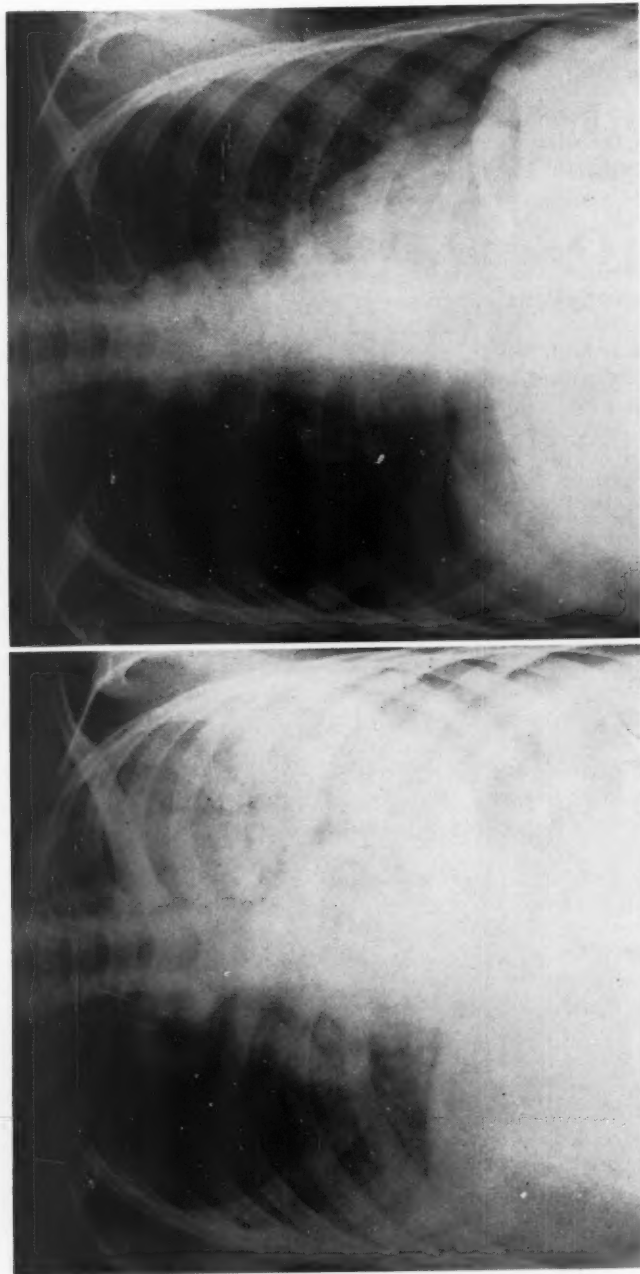


FIG. 5 (*left*). Three weeks after re-admission, recurrent infiltration has caused extensive consolidation on the left. Right costophrenic angle changes are residual of thoracotomy.

FIG. 6 (*right*). Six weeks after second admission, the discharge chest x-ray again shows complete regression of acute infiltration. Note residual adenopathy and increasing residual reticular fibrosis.

This is an iron stain, according to information supplied, and the blue color that we are looking at here is iron pigment.

Ventilation studies were repeated, and reduced values for maximal breathing capacity (MBC) and vital capacity (VC) were observed again.

There was a very basic physiologic defect in this young man. Weakness alone could contribute to this functional defect, but there had been an obvious loss of elasticity of the lungs, and there must have been some process permitting only a limited amount of oxygen to enter the blood.

Another episode developed, with cough, hoarseness and x-ray evidence of a mild increase in pneumonitis, and again there was a corresponding slight drop in hemoglobin. Corticosteroids promptly cleared this minor process, during which he was never dyspneic or cyanotic. Improvement was sufficiently good to permit his discharge to his home.

The patient's third admission was in February, 1958, following the appearance of acute illness. On arrival in the hospital he had labored, rapid breathing, and cyanosis. Laboratory examinations showed less anemia than he had had before, reticulocytes, 2%, and a slight polymorphonuclear leukocytosis.

X-ray examination of the chest showed marked changes.

DR. EMIL SCHULZ: The film obtained at the end of the patient's second admission shows clearing of the acute infiltration (figure 6) which was so prominent on the previous film (figure 5).

The last x-ray examination of the chest was obtained at the time of the patient's last admission to the hospital (figure 7). In the upper lobes the lesions are blotchy, soft and almost nodular in appearance. There is dense consolidation in the bases. Respiratory motion caused blurring and loss of detail.

DR. THEODORE L. BADGER: About 12 hours after the patient's admission his condition began to deteriorate, despite resumption of steroid therapy. He became extremely cyanotic, even in the oxygen tent. Two hours before death he passed dark urine, which was negative for bile but strongly positive for occult blood. No fresh red cells or red cell casts were seen on microscopic examination. Whatever the cause, this represented a paroxysmal hemoglobinuria without evidence of red blood cells, either bladder or renal in origin. There may have been renal ischemia, or infarction of a kidney, but neither condition explains the finding satisfactorily. One wonders whether this may not have been etiologically related to the previous episodes of hemoptysis and the apparent acute hemolytic anemia.

In summary, I do not know what this patient had, but it appears to be a physiologic rather than an infectious disorder. The episodes of illnesses were characterized by rather diffuse pulmonary opacification, which came and went with unusual rapidity and, until the end, were extraordinarily responsive to treatment with corticosteroids. Something had produced a restrictive process in the lungs, with loss of pulmonary elasticity and with a severe diffusional defect,<sup>5, 7</sup> but without evidence of emphysema or any obstructive element. I am not sure we should speak of alveolar-capillary block in this regard, a concept which may not always reflect the true pathologic lesion. I think it was Dr. Robert Austrian, at the Johns Hopkins, who described alveolar-capillary block as an obstruction to the flow of oxygen across the alveolar membrane, resulting in a decrease in the volume of oxygen which passes through the alveolar mem-

brane per minute per millimeter of mercury.<sup>5</sup> This represents an increase in the pressure gradient between alveolar  $O_2$  and pulmonary capillary  $O_2$ .

This boy's alveolar-capillary block<sup>5, 6</sup> may be pictured as a diffuse pulmonary fibrosis with a thickening of the alveolar wall, such as is seen in the Hamman-Rich<sup>11, 12</sup> syndrome, as well as in many other types of pulmonary fibrosis, such as beryllium disease<sup>13, 14</sup> and stonecutter's disease or silicosis. Also, the block

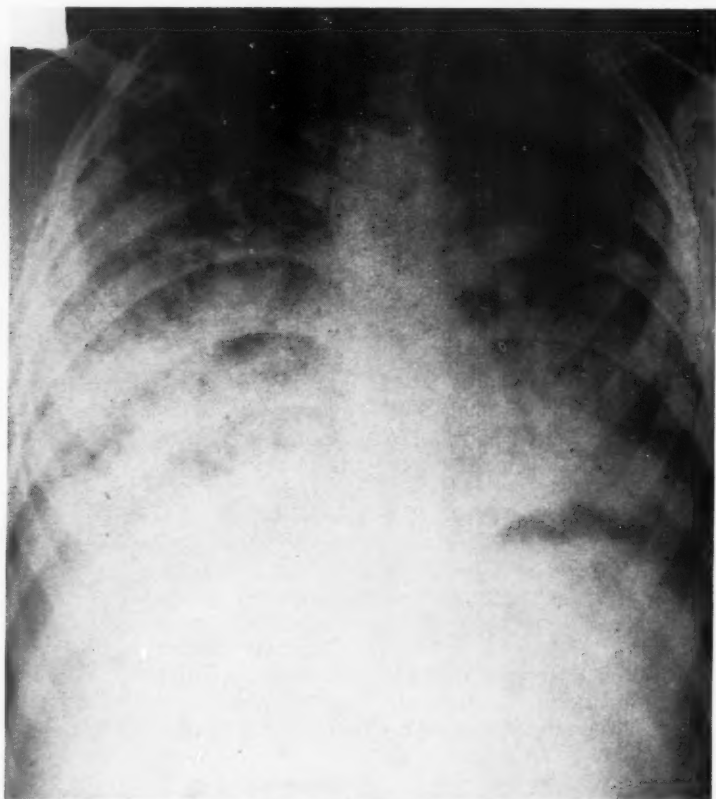


FIG. 7. The last chest film on third admission, seven weeks after discharge, shows blotchy, soft and some nodular lesions. Toward the bases, confluence of lesions with dense consolidation is noted.

could have been due to diminution in the capillary bed of the alveolar membrane, or to a loss of substance in the alveolar bed such as is seen in emphysema. Emphysema need not be considered here.

Pulmonary arterial occlusive disease in the precapillary areas<sup>4</sup> without infarction or involvement of the alveolar capillary bed could account for his extraordinary tachypnea, but this seems unlikely. Edema of the lungs alone does not seem to affect seriously the diffusional component of pulmonary function.



However, in pulmonary alveolar microlithiasis,<sup>15</sup> a disorder in which there are millions of minute stones filling alveolar spaces, there exists a characteristic physiologic alveolar capillary block, although the alveolar membranes are normal. But this does not seem to apply in this case.

The rather rapid appearance and disappearance of diffuse pneumonitis must be explained. Consider substances which could pour into the alveolar space. It could be blood, as it is rather rapidly absorbed, and in this case the speed of absorption may have been influenced by steroid therapy.

We might consider the deposition of hemoglobin from hemolyzed blood. Usually, under such circumstances, we find hemosiderosis. This does not quite fit the picture of hemosiderosis, despite the finding of hemosiderin granules in the macrophages. Hemosiderosis is a progressive disease and does not, in my experience, show the rapid alterations in the x-ray picture that we have seen in this case. I think that an outpouring of serum, as in cardiac decompensation or in allergic states, such as one would see in Loeffler's syndrome,<sup>16</sup> also really cannot explain this particular problem.

Sarcoidosis need not be considered. I have mentioned the Hamman-Rich syndrome<sup>11, 12</sup> because the physiologic changes, if they were more constant, would fit a picture of progressive interstitial fibrosis.

Other pulmonary diseases producing fine reticular or nodular lesions of the lung, such as beryllium disease, alveolar cell carcinoma, Loeffler's syndrome and pneumocystic pneumonia, will not be discussed, as they do not seem particularly applicable to this case.

My final diagnosis is pulmonary alveolar proteinosis.<sup>17</sup> In this disease there is an outpouring of clear, proteinaceous material into the alveoli, which have essentially normal membranes. Early, there is no ventilatory defect, but measurable slowing does develop, due apparently to the protein-filled alveoli. The degree of pulmonary dysfunction progresses in a fashion similar to that in cases with a primary membranous defect. It is usually fatal, but cases are beginning to appear where rapid improvement has been noted when death seemed imminent. The etiology of alveolar proteinosis is unknown, but it appears to be a physiologic disease, the pathogenesis of which is uncertain because of lack of understanding of the dynamics of the pulmonary circulation.

May we now please see the biopsy of the lung?

This biopsy of the lung shows some thickening of the alveolar membrane and an iron pigment, which I suppose is hemosiderin scattered widely throughout.

The biopsy of the lung convinces me of the errors of my deductions. This would seem to be a case of idiopathic pulmonary hemosiderosis of the lung, rather than idiopathic pulmonary alveolar proteinosis.

Never before in my fairly long association with the pulmonary aspects of internal medicine have I seen anything like this case. Hemosiderosis associated with mitral stenosis and multiple transfusions is a rare condition. In children, hemosiderosis is most often a chronic, progressive disease, which might in x-ray appearance be similar to pulmonary alveolar microlithiasis. In the early stages, the x-ray findings may be similar to those seen in pulmonary alveolar proteinosis, with its fine reticular pattern. But the clinical course of this case of hemosiderosis seems unique.

DR. VERNON KNIGHT: Thank you very much, Dr. Badger.

Dr. Suskind, Clinical Center Pathological Anatomy Department, will report the findings at autopsy and present an analysis of the case.

DR. R. GERALD SUSKIND: Customarily, the pathologist is supposed to supply the answers in exercises of this type. If the questions asked are, Can you give a name to this disease? Has it been seen before? Then we can supply the answer, and it has been correctly deduced by Dr. Badger. This patient suffered and died from a well described, poorly understood, rare, clinicopathologic entity to which the name of idiopathic pulmonary hemosiderosis has been given. Perhaps the name is unfortunate, because the hemosiderosis is not really idiopathic, but is a consequence of repeated pulmonary hemorrhages, the nature of which is obscure.



FIG. 8. Smear of bronchial washing stained with Prussian blue. Note the prominent hemosiderin-laden macrophages.

The main clinical and diagnostic features of this disease are illustrated in this case and have just been eloquently presented. The majority of published cases occur in the pediatric age group, or have their onset in childhood. The disease is characterized by episodic bouts of intra-alveolar hemorrhage associated with dramatic symptoms of dyspnea, cyanosis and varying degree of hemoptysis, usually accompanied by iron deficiency anemia. The outcome usually is death within a number of years due to progressive respiratory insufficiency or chronic cor pulmonale; however, long periods of remission are known to occur. Massive hemorrhage is rare, and clinical evidence of alveolar or bronchiolar hemorrhage is often confined to insignificant expectorations of "rusty sputum," or, persistence of large numbers of hemosiderin-laden macrophages in bronchial washings or gastric aspirations (figure 8). The diagnosis

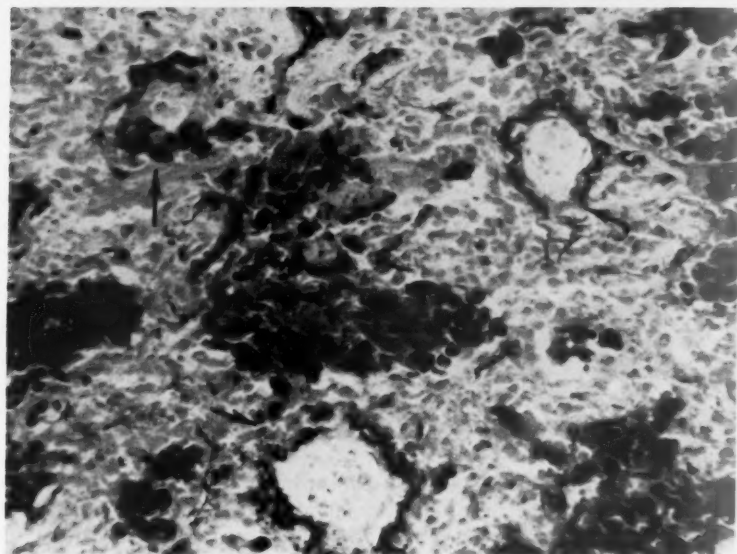
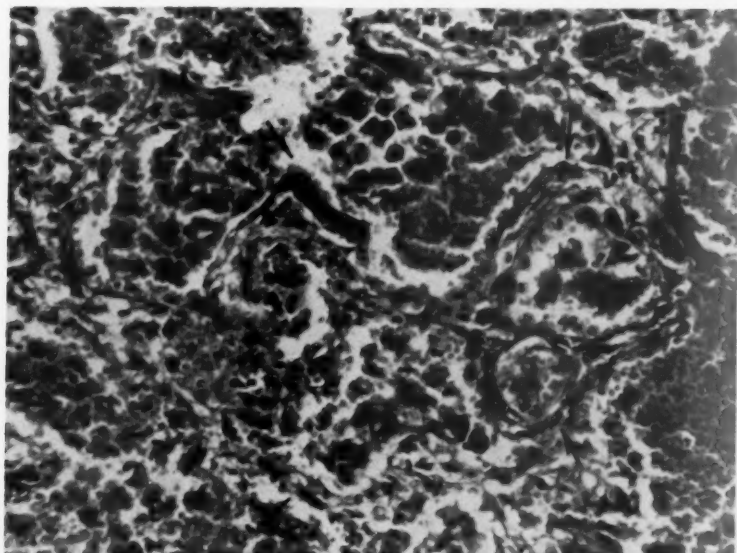


FIG. 9 (*above*). Lung, elastic v. Gieson, 210  $\times$ .

FIG. 10 (*below*). Lung, iron-orcein. Arrows point to fragmentation and iron incrustation of elastic fibers, chiefly of arterioles and veins. 210  $\times$ .

may be suspected clinically and radiographically, but usually is difficult without histologic confirmation.

Both the lung biopsy and the autopsy findings in the lung illustrate the characteristic histologic features of advanced stages of the disease process, which is one of hemorrhage and a specialized tissue reaction thereto, as was first clearly recognized by Ceelen in 1931.<sup>18</sup> In figures 9 and 10 the alveolar spaces and bronchioles are obliterated by hemosiderin, hemosiderin-laden macrophages



FIG. 11. Cut surface of lung exhibits prominent lobular markings and thickened alveolar walls. The consistency was increased, but there was no fibrosis along the larger bronchi or vessels. The cut surface was mottled red and brown.

and red blood cells. There is a marked thickening and fibrosis of the alveolar walls, with fragmentation and iron incrustation of elastic fibers, and secondary foreign-body giant cell reaction both of alveolar septa and particularly of small blood vessels. Each of the numerous sections examined showed similar changes.

At autopsy, the gross appearance of the lungs was distinctive. They weighed 1,100 gm., which is more than three times the mean weight for the age, were rusty brown and of hepatic consistency; aeration was absent (figure 11). Except for secondary hypertrophy of the right ventricle, no major pathologic

findings were noted. Hemosiderin deposition was confined to the lungs and tracheobronchial lymph nodes.

Almost nothing is known about the pathogenesis of this disease process, and speculation is usually based on isolated case reports. Ceelen<sup>18</sup> was the first to note the fragmentation of elastic fibers and iron incrustation, principally in the small arterioles and venules. He postulated an abnormality of elastic fibers as the basis of this hemorrhage. Morphologic examination of this and similar cases seems to support the view that hemorrhage has occurred in these areas. A colored latex perfusion of the pulmonary arteries and pulmonary veins of the right lower lobe was performed in this case in the hope of determining the site of hemorrhage. Surprisingly, a very fine arborization of both the pulmonary arterial and the venous systems was obtained after digesting the remaining lung tissue. Unfortunately, the bronchial arterial tree was not injected, a procedure which might be attempted on a future occasion. The hypothesis of a primary elastic tissue defect as a cause of hemorrhage is weakened by observations that this elastic tissue fragmentation is not present in early stages of this disease.<sup>21, 22, 23</sup> It has been observed also in some cases of severe pulmonary hemosiderosis associated with mitral stenosis,<sup>24</sup> and may be the result, rather than the cause of hemorrhage. Propst,<sup>20</sup> in histochemical and electronmicrographic studies of two cases, claims to have demonstrated an acid mucopolysaccharide ground substance surrounding elastic fibers acting as a substrate for iron salts and hemosiderin. Such a finding could not be confirmed in this case.

Studies by Apt<sup>25</sup> and coworkers of ferrokinetics with Fe<sup>59</sup> and erythrocyte survival studies with erythrocytes labeled with Cr<sup>51</sup> and Ashby counts have failed to show abnormalities not explained by a rapid turnover, secondary to hemorrhage.

The episodic character of these hemorrhages is puzzling. In this connection, the observed rise in cold agglutinin titer to the patient's own red blood cells during a period of crisis is interesting, and invites further confirmation<sup>19</sup> before speculating on a hypothetic auto-immune mechanism. It is hoped that an early recognition of this idiopathic disease will help in the accumulation of needed information.

DR. VERNON KNIGHT: I should like to thank Dr. Badger for his excellent discussion. The meeting is adjourned.

#### SUMMARY IN INTERLINGUA

Iste Conferentia Clinico-Pathologic se concerneva con un caso de recurrente morbo pulmonar in un patiente pediatric. Le curso clinic esseva characterisate per symptomatas e signos de repetite bronchitis, con episodios sporadic de hemoptysis. Le patiente esseva de basse statura relative a su etate, se fatigava facilmente, e esseva anemic. Acute morbos intercurrente esseva severmente prostatori, sed le patiente respondeva promptemente al therapia a hormon adrenal. Durante un periodo de pejoration clinic, repetite examines roentgenologic del thorace monstrava extense infiltratos maculate in omne partes del campos pulmonar, particularmente in le regiones perihilar. Un resolution rapide de iste infiltratos occurreva durante tempores de melioration clinic, sed residue alterationes reticular e lymphadenopathia hilar persisteva.

A parte le intense investigation clinico-laboratorial, biopsias de nodo lymphatic e de tissu pulmonar esseva effectuate. Le constatationes laboratorial e le diagnose differential es discutite.

Le pathologo presenta le constatationes necroptic e un analyse de iste inusual e paucio comprehendite morbo, i.e. idiopathic hemosiderosis pulmonar.

#### BIBLIOGRAPHY

1. Gitlin, D., Hitzig, W. H., and Janeway, C. A.: Multiple serum protein deficiencies in congenital and acquired agammaglobulinemia, *J. Clin. Investigation* **35**: 1199, 1956.
2. di Sant'Agnese, P. A.: The pulmonary manifestations of fibrocystic disease of the pancreas, *Dis. of Chest* **27**: 654, 1955.
3. Conant, N. F., Smith, D. T., Baker, R. D., Callaway, T. L., and Martin, D. S.: *Manual of clinical mycology*, 2nd Ed., 1954, W. B. Saunders Company, Philadelphia, pp. 149-168.
4. Conant, Smith, Baker, Callaway and Martin, op. cit., pp. 119-149.
5. Austrian, R., McClement, J. H., Renzetti, A. D., Jr., Donald, K. W., Riley, R. L., and Cournand, A.: Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion, *Am. J. Med.* **11**: 667, 1951.
6. Bader, M. E., and Bader, R. A.: The alveolar-capillary block syndrome (Editorial), *Am. J. Med.* **24**: 493, 1958.
7. Cournand, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary disease, The fourth Walter Wile Hamburger memorial lecture, Institute of Medicine of Chicago, *Circulation* **2**: 641, 1950.
8. Gaensler, E. A.: Clinical pulmonary physiology, *New England J. Med.* **252**: 177, 221, and 264, 1955.
9. Comroe, J. H., Forster, R. E., Dubois, A. B., Briscoe, W. A., and Carlsen, E.: *The lung: clinical physiology and pulmonary function tests*, 1955, Yearbook Publishers, Inc., Chicago.
10. West, W. O.: Acquired hemolytic anemia secondary to Boeck's sarcoid, *New England J. Med.* **261**: 688, 1959.
11. Hamman, L., and Rich, A. R.: Fulminating diffuse interstitial fibrosis of lungs, *Tr. Am. Clin. and Climatol. A.* **51**: 154, 1935.
12. Hamman, L., and Rich, A. R.: Acute diffuse interstitial fibrosis of lungs, *Bull. Johns Hopkins Hosp.* **74**: 177, 1944.
13. Gaensler, E. A., Verstraeten, J. M., Weil, W. B., Cugell, D. W., Marks, A., Cadigan, J. B., Jones, R. H., and Ellicott, M. F.: Respiratory pathophysiology in chronic beryllium disease, *Arch. Indust. Health* **19**: 132, 1959.
14. Hardy, H. L.: Differential diagnosis between beryllium poisoning and sarcoidosis, *Am. Rev. Tuberc. and Pul. Dis.* **74**: 885, 1956.
15. Badger, T. L., Gottlieb, L., and Gaensler, E. A.: Pulmonary alveolar microlithiasis, or calcinosis of the lungs, *New England J. Med.* **253**: 709, 1955.
16. Crofton, J. W., Livingstone, J. L., Oswald, N. C., and Roberts, A. T.: Pulmonary eosinophilia, *Thorax* **7**: 1, 1952.
17. Rosen, S. H., Castleman, B., Liebow, A. A., Enzinger, F. M., and Hunt, R. T. N.: Pulmonary alveolar proteinosis, *New England J. Med.* **258**: 1123, 1958.
18. Ceelen, W.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Vol. III/3, 1931, J. Springer, Berlin, p. 20.
19. Wyllie, W. A., Sheldon, W., Bodian, M., and Barlow, A.: Idiopathic pulmonary hemosiderosis, *Quart. J. Med.* **17**: 25, 1948.
20. Propst, A.: Morphologie und Pathogenese der essentiellen Lungenhämosiderose, *Virchows Arch. f. path. Anat.* **326**: 633-663, 1955.



21. Smith, W. E., and Fienberg, R.: Early nonrecurrent idiopathic pulmonary hemosiderosis in an adult, *New England J. Med.* **259**: 808, 1958.
22. Soergel, K. H.: Idiopathic pulmonary hemosiderosis: review and report of two cases, *Pediatrics* **19**: 1101-1108, 1957.
23. Browning, J. R., and Houghton, J. D.: Idiopathic pulmonary hemosiderosis, *Am. J. Med.* **20**: 374-382, 1956.
24. Lendrum, A. C.: Pulmonary hemosiderosis of cardiac origin, *J. Path. and Bact.* **62**: 555-561, 1950.
25. Apt, L., Pollycove, M., and Ross, J. F., with the technical assistance of Pratt, M., Sullivan, J., and Donovan, J.: Idiopathic pulmonary hemosiderosis. A study of the anemia and iron distribution using radioiron and radiochromium, *J. Clin. Investigation* **36**: 1150-1159, 1957.

## CASE REPORTS

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### WATERHOUSE-FRIDERICHSEN SYNDROME IN VARICELLA \*

By ROBERT R. MONTGOMERY, M.D., *Washington, D. C.*  
and MAGNUS OLAFSSON, M.D., *Reykjavik, Iceland*

THE Waterhouse-Friderichsen syndrome typically appears early in the course of severe meningococcic infection, and usually leads swiftly to death. It is characterized by shock, prostration, purpura, and massive hemorrhage into the adrenal glands. Until the advent of sulfonamides, antibiotics and, later, adrenal corticosteroids, it was usually fatal; indeed, if a patient survived, the accuracy of the diagnosis was questioned.

Since its initial description and later clinical definition, it had been reported as occurring in the course of various other infectious diseases. As far as we can determine after an extensive review of the literature, the following case is the first report of its occurrence with chickenpox.

#### CASE REPORT

A 33 year old white male first noticed an eruption on his torso on June 3, 1957. He stayed home from work during the next three days, feeling that he had chickenpox. (He had been exposed to this disease through his fiancée's two children, who had developed the disease successively during the preceding three weeks.) Treatment during this phase consisted only of salicylates and calamine lotion. On June 7 he felt somewhat feverish on arising. Later in the day he became worse, and was found to have a temperature of 104° F. As the evening progressed he became cold and clammy, and began to breathe quite rapidly. He was seen at home at approximately 11 p.m. by one of us. At that time he was very restless and generally hot, but had cold, moist feet. His face was extremely ruddy, and his feet and hands were mottled and bluish. The skin blanched readily under pressure, but regained its color slowly. Blood pressure was 60/40 mm. Hg; pulse, 140; respiration, 40 per minute. There were many vesicular lesions, characteristic of chickenpox, over the entire trunk. They presented all stages of development, from early, small, papular lesions up to and including umbilicated and crusted vesiculae. No lesions were found on the palms of the hands or the soles of the feet. The palate and posterior oropharynx were quite red. Several pea-sized posterior cervical lymph nodes were felt bilaterally. One walnut-sized node was present in the right axilla, and the contiguous area of the anterior thorax was red, edematous and tender. The edge of this lesion was fairly sharp, suggesting erysipelas. The heart was not enlarged, and was regular at a rate of 140 per minute. The sounds were distant. There were no murmurs. The lungs were clear throughout. The abdomen was soft and non-tender, and presented no palpable masses. Deep tendon reflexes were all normal. Babinski's reflexes were normal.

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Requests for reprints should be addressed to Robert R. Montgomery, M.D., 1746 K Street, Northwest, Washington, D. C.

After the patient's admission directly to the Emergency Room of Emergency Hospital, the following laboratory studies were obtained: hemoglobin, 15.5 gm.; hematocrit, 49.8%; white blood count, 25,800; polymorphonuclear neutrophils, 90%; lymphocytes, 10%; sedimentation rate, 16 mm. per hour; blood sugar, 162 mg./100 c.c.; CO<sub>2</sub> combining power, 42 vol.%; blood chloride, 78 mEq./L.; total eosinophils, 22.

Immediately after the blood was drawn for the laboratory studies the patient was given 1,000 ml. of glucose in saline intravenously, followed by 1,000 ml. of 10% glucose in water. Each liter contained 100 mg. of hydrocortisone sodium succinate and 1,000,000 units of crystalline penicillin G. Oxygen was begun by nasal catheter. Phenobarbital was used for sedation. During the ensuing three hours the patient improved both subjectively and objectively. His blood pressure at 5 a.m. was 100/60 mm. of Hg, and he was more comfortable. He had three loose stools during the first three hours, each of which contained a moderate amount of greenish mucoid material.

The next three hours showed general deterioration, and by 8 a.m. the blood pressure was 80/50 mm. of Hg; pulse, 145; respiration, 45 per minute; temperature 104.2° F. The skin at that time was warm and dry. Another 1,000 ml. of 5% glucose in saline were given. This also contained 100 mg. of hydrocortisone sodium succinate and 1,000,000 units of crystalline penicillin. It was felt at this time that the patient probably had a complicating bacterial infection which had caused the area of inflammation around the axilla and which was also intensifying his prostration. Levarterenol bitartrate, 4 c.c. in 1,000 ml. of 10% glucose in water, was begun intravenously. The blood pressure, however, remained below 90 mm. Hg systolic until another 4 c.c. of levarterenol bitartrate were added to the solution. This infusion also contained 1,000,000 units of crystalline penicillin and 100 mg. of hydrocortisone sodium succinate.

Shortly after noon, the patient's temperature rose to 107° F. and his restlessness became intense. The extent of his evident illness is indicated by these observations (2:30 p.m.): "His temperature is 107°. His pulse and pressure are unobtainable in spite of the steady flow of nor-epinephrine into his veins. Though constantly receiving oxygen, he is deeply cyanotic and desperately dyspneic. He is tragically lucid. His restlessness has now gone and all effort is being used in a fruitless attempt to get enough air. Though his dyspnea keeps him from speaking, he looks constantly at me with fearful, pleading eyes." Twenty minutes later the patient died.

Postmortem examination showed a bluish purple, macular discoloration of the skin of the face, ears, neck, shoulders and upper arms. Many small, crusted lesions showed the classic changes of varicella. The left pleural cavity contained approximately 500 c.c. of clear fluid, and the pericardium contained approximately 100 c.c. of clear fluid. The lungs were heavy, weighing 900 and 970 gm. Both were rubbery in consistency, congested and engorged. Microscopically, pulmonary edema was found. The spleen was normal and enlarged, weighing 325 gm. Both adrenal glands were almost completely replaced by hemorrhage. Bacteriologic studies included blood culture during life, and postmortem cultures from venous blood and from the red, raised area covering the left axilla and extending on to the anterior thorax. All of these cultures were negative. In addition, direct smears were made from the skin, the ileum, and the anterior chest wall. All of these smears showed protein material and various types of debris, but none showed any bacteria. The conclusion of the pathologist was: varicella with massive adrenal hemorrhage and pulmonary edema. All of the other changes were felt to be due to diffuse inflammatory infiltration.

#### DISCUSSION

Deaths from varicella in adults are rare. In most of those reported, pneumonia has been the fatal complication. The largest series of cases with

this complication contained 12 patients, three of whom died.<sup>1</sup> Search for cases presenting the Waterhouse-Friderichsen syndrome has been fruitless. Three cases, however,<sup>2, 3, 4</sup> have presented the clinical picture of shock along with their pneumonia. One<sup>4</sup> was treated with corticosteroids and recovered. In the other two, postmortem examination was performed and did not show adrenal hemorrhage. Whether adrenal insufficiency without actual hemorrhage played a part in the production of shock in these patients is a speculative question which cannot be accurately answered.

The term "Waterhouse-Friderichsen syndrome" has been used since its coinage in 1933<sup>5</sup> to include cases of fulminant septicemia in the course of meningococcal infection, and to describe those cases that present the picture of adrenal failure and peripheral circulatory collapse. These cases have usually shown massive hemorrhage into the adrenal glands at autopsy. However, variations of this syndrome have been recognized and classified.<sup>6</sup> These variations include the clinical picture of Waterhouse-Friderichsen syndrome without adrenal hemorrhage (in autopsied cases)<sup>7</sup>; the syndrome occurring in diseases other than meningococemia; and clinical Waterhouse-Friderichsen syndrome with recovery (which eliminates the possibility of demonstrating adrenal hemorrhage). The case presented here had a clinical picture consistent with this diagnosis, and also presented hemorrhage into the adrenal glands at autopsy. It occurred, however, in the course of chickenpox rather than of meningococemia.

Experience with the treatment of Waterhouse-Friderichsen syndrome has led to a more encouraging prognosis than has been entertained in the past. Vigorous treatment with antibiotics, adrenal corticosteroids, norepinephrine and other supportive measures has led to recovery in a progressively larger percentage of cases. Kanter et al.<sup>8</sup> have recently reported a series of 10 cases, five of whom survived.

#### SUMMARY

A case of Waterhouse-Friderichsen syndrome in an adult with varicella is presented. The clinical course and the findings at autopsy confirmed the diagnosis.

#### ACKNOWLEDGMENT

Our thanks are extended to Dr. Worth B. Daniels, who saw the patient in consultation and guided us in the preparation of this report.

#### SUMMARY IN INTERLINGUA

Un caso de varicella in un masculo de 33 annos de etate se initiava typicamente e se terminava letalmente con le tableau clinic de colapso vascular profunde.

Le tractamento consisteva in effortios de mantener le volumine de liquido e le administration de hydrocortisona a succinato de natrium (dosage total: 400 mg) a bitartrato de levarterenol. Esseva etiam administrate penicillina pro eliminar omne infection secundari (dosage total: 4,000,000 unitates).

In despecto de un intense therapia, le tension sanguinee del patiente remaneva basse. Ille moriva in choc profunde 13 horas post su hospitalisation. Le necropsia confirmava le diagnose de varicella. Illo demonstrava massive hemorrhagia in ambe adrenales, establente assi le diagnose de syndrome de Waterhouse-Friderichsen.

Casos mortal ab varicella in adultos es rar. Usualmente le complication mortal es pneumonia, ben que casos con statos de choc clinic se trova reportate. Es opinat que le presente reporto es le prime de syndrome de Waterhouse-Friderichsen in iste morbo.

## BIBLIOGRAPHY

1. Fitz, R. H., and Meiklejohn, G.: Varicella pneumonia in adults, *Am. J. M. Sc.* 232: 489-499, 1956.
2. Claudy, W. D.: Pneumonia associated with varicella, *Arch. Int. Med.* 80: 185-192, 1947.
3. Eisenbud, M.: Chickenpox with visceral involvement, *Am. J. Med.* 12: 740-746, 1952.
4. Rosencan, M., Baumgarten, W., Jr., and Charles, B. H.: Varicella pneumonia with shock and heart failure, *Ann. Int. Med.* 38: 830-845, 1953.
5. Glanzman, E.: Beitrag zur Klinik Hämatologie und Pathologie des Syndroms von Waterhouse-Friderichsen, *Jahrb. f. Kinderh.* 139: 49-63, 1933.
6. Pronove-Irreverre, P.: Waterhouse-Friderichsen syndrome. A review of the literature and a report of two cases of fulminating meningococcic septicemia, *Clin. Proc. Child. Hosp.* 10: 41-54, 1954.
7. Daniels, W. B.: Cause of death in meningococcic infection, *Am. J. Med.* 8: 468-473, 1950.
8. Kanter, D. M., Mauriello, D. A., and Learner, N.: Acute meningococcemia with vascular collapse: an analysis of 10 recently treated cases, *Am. J. M. Sc.* 232: 674-687, 1956.

### IDIOPATHIC PULMONARY HEMOSIDEROSIS: AN ADULT CASE WITH ACUTE ONSET, SHORT COURSE AND SUDDEN, FATAL OUTCOME \*

By H. BRUCE DENSON, M.D., *New Haven, Connecticut*

PULMONARY hemosiderosis, a disease of unknown etiology, is considered to be uncommon in children and rare in adults. The first description was given by Virchow in 1851, but it was not until 80 years later, in 1931, that Ceelen published the first clinical report. Clinical, roentgenologic and pathologic correlations were presented in 1944 by Waldenström<sup>1</sup> and in 1948 Wyllie et al.<sup>2</sup> published a review of the subject. Browning and Houghton<sup>3</sup> mentioned three adult cases and added three of their own, while Soergel,<sup>4</sup> in a more recent survey, culled 12 authenticated adult cases from the literature.

Numerous authors have noted that the disease is generally recurrent in nature, a rapid course being uncommon. The following case is considered to be worthy of note since, from a clinical, laboratory and pathologic point of view, it typifies this apparently rare disease entity. It is of unusual interest in that the patient had an acute onset of symptoms, a short course, and an unexpected, sudden death.

\* Received for publication April 2, 1959.

From the Irwin U. S. Army Hospital, Fort Riley, Kansas.

Requests for reprints should be addressed to H. Bruce Denson, M.D., Yale-New Haven Medical Center, Grace-New Haven Hospital, 789 Howard Avenue, New Haven, Connecticut.

## CASE REPORT

A 28 year old white male was hospitalized because of the acute onset of anorexia, fatigue, and cough productive of blood-streaked sputum. He had been well until three days prior to admission, when he noted the onset of slight cough productive of small amounts of white sputum. His appetite decreased and he felt himself to be febrile, though he did not record his temperature. On the following day he noted bright red blood streaking the sputum. He denied chest pain, dyspnea, chills or previous hemoptysis. He was seen at this time and admission was advised.

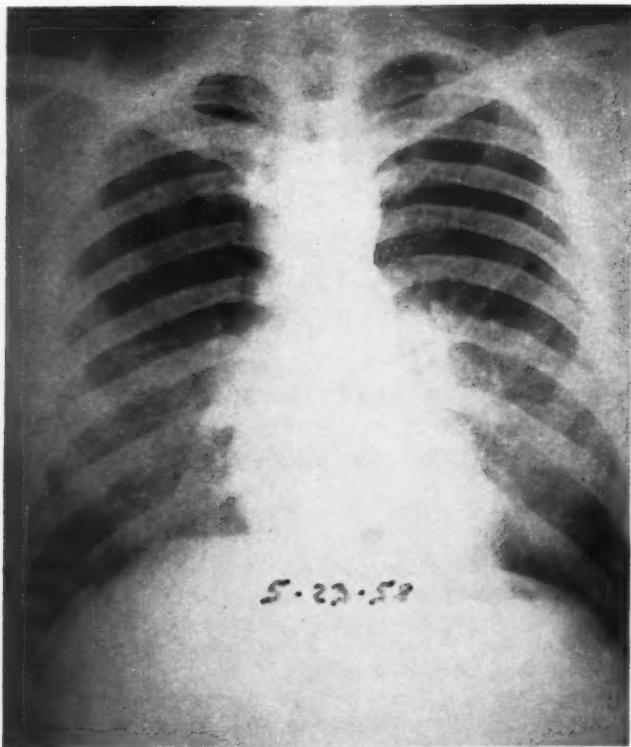


FIG. 1. Roentgenogram of the chest, showing ill defined, patchy, mottled densities in the lower lung fields bilaterally.

*Physical examination* revealed a well developed, pale white male who appeared to be acutely ill. Temperature, 101.8° F.; pulse, 104; respirations, 22; blood pressure, 100/60 mm. of Hg. There were scleral icterus and pallor of the conjunctivae and mucous membranes. Scattered moist râles were present at the right lung base. There was no lymphadenopathy. No abdominal organs were palpable. The remainder of the examination was within normal limits.

*Laboratory examination* revealed a hematocrit of 23%, hemoglobin of 7.3 gm., white blood count of 12,400, with a normal differential, and a platelet count of 213,500. There were marked hypochromia, slight anisocytosis, poikilocytosis and polychroma-



tophilia on smear. The reticulocyte count was 4.2%. Urinalysis and serology were normal. Coombs' test was negative, and the osmotic and mechanical fragility were normal. Sickle cell and L.E. cell preparations were negative. The serum bilirubin was 2.2 mg.%, with 2.0 mg.% in the indirect fraction. Cold agglutinins were negative, and clot retraction and hemoglobin electrophoresis were normal. Urine urobilinogen was positive in 1:10 dilution, and stool guaiac tests were negative to weak-positive. The serum iron was 22  $\mu$ g.%, and the iron-binding capacity was 432  $\mu$ g.%. Bone marrow was unremarkable. Cultures of the throat and sputum were unrevealing.

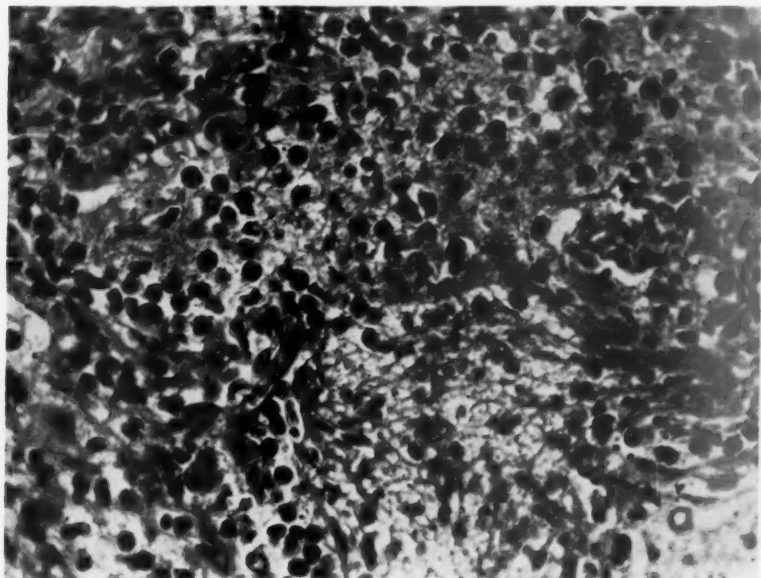


FIG. 2. Photomicrograph (hematoxylin and eosin stain,  $\times 440$ ), showing the alveoli filled by a mixture of edema fluid, red cells and large, round macrophages with pigment granules in their cytoplasm.

Roentgenograms of the chest disclosed ill defined, patchy densities in the lower lung fields bilaterally, felt to be compatible with a pneumonitis (figure 1). Gastrointestinal series and barium enema were unremarkable.

*Course:* The patient was treated symptomatically. His chest x-ray showed gradual improvement and his hemoptysis decreased after several days, but he continued to run a low grade fever. Diagnostic studies were carried out as noted, and he was started on intramuscular iron therapy. Despite this, no apparent change in his hemoglobin was noted. One morning during the sixth week of his illness he suffered a recrudescence of severe cough, with increasing hemoptysis and marked dyspnea. He was given oxygen, with some relief, but suddenly had a massive pulmonary hemorrhage and died.

*Autopsy Findings:* Significant findings at postmortem examination were limited to the lungs; the heart, liver and spleen were grossly and microscopically normal in all respects.

The left lung weighed 1,265 gm., the right, 1,205 gm. The pleurae were smooth

and glistening, with a diffuse, reddish purple mottling involving most of the surface. On palpation they felt subcrepitant. On sectioning, the parenchyma had a uniform, mottled reddish to purple appearance, no discrete lesions being noted. On pressure, large amounts of blood and frothy edema fluid were expressed from the cut surfaces.

Microscopically, sections from various lobes of both lungs showed a similar picture. There was an over-all lack of aeration, most of the alveoli being filled by a mixture of edema fluid, red blood cells and large, round macrophages, with brown to brick-red pigmented cytoplasm (figure 2). In scattered areas a few polymorphonuclear leukocytes were noted within the alveoli, and there was also a patchy interstitial infiltration of these cells. A few alveoli showed thickening of the walls by fine collagenous fibers, but this change was not widespread.

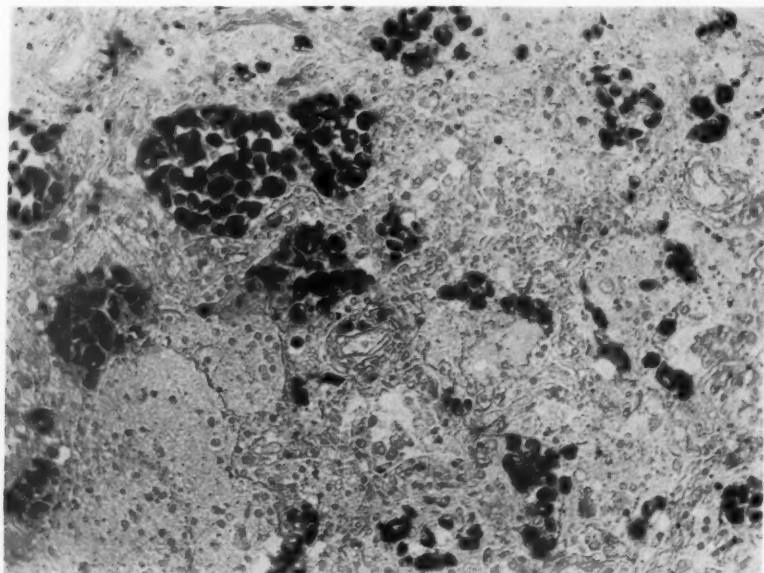


FIG. 3. Photomicrograph (iron stain,  $\times 180$ ), showing large macrophages laden with deep blue staining granules of hemosiderin completely filling several alveoli.

Special stains revealed the cytoplasm of the histiocytes to be strongly positive for iron (figure 3). These cells were found scattered throughout the sections, as well as in masses completely filling many alveoli.

#### DISCUSSION

Characteristically, idiopathic pulmonary hemosiderosis in the adult presents with cough, hemoptysis, fever, dyspnea and tachycardia, resembling in many respects an acute respiratory infection. Roentgenograms of the chest most commonly reveal diffuse, mottled opacities with reticular design resembling those seen in a viral pneumonia.<sup>5</sup> These are usually basilar, but may radiate out from the hilum, suggesting early pulmonary edema. As time progresses, pallor becomes more prominent, and the patient may become frankly icteric.

Laboratory studies disclose a hypochromic microcytic anemia, often severe,

with anisocytosis and poikilocytosis on smear, and a reticulocytosis. A leukocytosis may be present. Bilirubinemia, predominantly in the indirect fraction, and the excretion of excess amounts of urobilinogen are often present, suggesting a hemolytic process, but serum iron and iron-binding capacity are characteristic of a severe iron deficiency anemia. This seemingly paradoxical finding is strikingly demonstrated by this patient. Its occurrence may be explained on the basis of repeated intra-alveolar hemorrhage with re-absorption of the breakdown products of the red blood cells.

The sputum during the acute episode characteristically contains hemosiderin-filled macrophages ("siderophages"). The pigment in the cytoplasm of these cells appears as clumps of yellow-brown granules that stain a deep blue with the Prussian blue reaction of potassium ferrocyanide and hydrochloric acid.

Should a remission occur during this period, the patient will usually manifest mild chronic cough, fatigue, pallor with persistent anemia, and minor attacks of hemoptysis. Occasionally in the recurrent form of the disease clubbing of the fingers, cardiomegaly, hepatomegaly, splenomegaly and lymphadenopathy will develop.

Soergel<sup>4</sup> reported the extremes of the clinical course as being from five weeks to 10 years, with a mean duration of life of 2.9 years in fatal cases. Smith and Fienberg<sup>6</sup> recently reported an adult who died within six weeks of the onset of symptoms. They stressed the extreme rarity of a short, nonrecurrent course.

All authors agree that the acute attack is precipitated by sudden and severe intra-alveolar hemorrhage. However, the etiology of the disease remains controversial, various theories having been proposed.<sup>7,8</sup> Consideration has been given to a circulatory defect causing pressure imbalance at capillary anastomoses, as well as to the possibility of a defect in vasomotor control of the lesser circulation, with diapedesis of red blood cells. However, evidence to substantiate these hypotheses is lacking. The histology of the pulmonary parenchyma has suggested a defect in elastic and other supporting tissues, but similar microscopic findings have been found in brown induration associated with mitral stenosis; also, abnormalities of the elastic tissue have not been a constant finding.<sup>6,9</sup>

An allergic etiology has been suggested by Steiner,<sup>10</sup> who found that splenectomy terminated the attacks in a six year old boy. Of possible relevance are two cases with apparent remission associated with the use of steroids.<sup>3,14</sup>

Detailed pathologic examinations have been made in several fatal cases,<sup>2,3,11</sup> the characteristic findings being those present in the lungs. The alveoli are filled with hemosiderin-laden macrophages and fresh red cells. In the acute case, this may be the only finding. In the recurrent form, the elastic fibers of the alveolar septa and the elastic lamina of the small and medium-sized arteries become impregnated with hemosiderin, and may become coarse and fragmented, and undergo degeneration. In the case reported here this finding was not present, in keeping with the short course of this patient's illness. In the prolonged case, cor pulmonale may develop, and the pulmonary arteries may be tortuous and sometimes thickened. Soergel<sup>4</sup> reported that 70% of the cases he reviewed had hypertrophy and dilatation of the right ventricle. The absence of hemosiderin in other organs has been a uniform finding.

Smith and Fienberg<sup>6</sup> note that the diagnosis of idiopathic pulmonary hemosiderosis is relatively easy in the chronic case but much more difficult in the

acute form. Though this is a valid generalization, successful diagnosis in the acute case, as typified by this patient, seems quite possible if one is cognizant of the significance of the coincidental appearance of respiratory symptoms with hemoptysis and a severe iron deficiency anemia that frequently manifests hemolytic features. Confirmatory, and practically diagnostic, is the finding of hemosiderin-laden macrophages in the sputum in the absence of other causes of passive congestion of the pulmonary bed. With a view to ancillary diagnostic aid, it is to be noted that Gellis et al.<sup>13</sup> have performed successful needle biopsy of the lung in four cases.

Awareness of the condition so that early diagnosis may be facilitated is of utmost importance. Only then can attempts be made at therapy beyond mere supportive measures. It should be reemphasized that two cases<sup>3,14</sup> subjected to a trial of steroids have responded favorably, and that Soergel<sup>4</sup> has reported two patients who did well following splenectomy.

It is hoped that, with greater awareness and hence early recognition, opportunity for study of etiologic mechanisms may be afforded and therapy further evaluated.

#### SUMMARY

An acute, fatal case of idiopathic pulmonary hemosiderosis occurring in an adult is presented. The patient is of interest because of the apparent rarity of this disease, particularly in the adult, and because of the nonremitting nature and short duration of his illness.

The clinical, laboratory and pathologic findings in this disease have been reviewed, and are sharply demonstrated by the patient presented. Diagnosis is discussed and the hope expressed that, with greater awareness, opportunity for further study will be afforded.

#### SUMMARIO IN INTERLINGUA

Un acute, non-recurrente caso mortal de hemosiderosis pulmonar con le classic constataciones laboratorial e pathologic es presentate. Le morbo ha un etiologia non cognoscite. Il pare que illo es rar, specialmente in adultos.

Le patiente esseva un masculo de racia blanc de 28 annos de etate qui se presentava con anorexia, fatiga, e hemoptysis. Ille monstrava febre, pallor, ictero scleral, e rhonchos al base dextero-pulmonar. Studios laboratorial revelava sever anemia, leucocytosis, reticulocytosis, e bilirubinemia (predominantemente del typo indirecte). Tamen, le ferro seral esseva 22, le capacitate ferro-ligatori 432  $\mu\text{g}\%$ . Le medulla ossee, le test de Coombs, e studios de fragilitate contribueva nulle information. Le mesmo valeva pro culturaciones del sputo. Roentgenographias thoracic revelava mal-definite densitates in le campos infero-pulmonar a ambe lateres.

Le patiente esseva tractate symptomaticamente. Ille etiam recipiva ferro intramuscular. In despecto de iste effortios, le anemia non se meliorava e le constataciones thoracic persisteva, sed subjectivamente le patiente se sentiva melio. In le curso del sexte septimana del morbo, ille suffreva un massive hemorrhagia pulmonar e moriva. Le constataciones significative del necropsia esseva restringite al pulmones. Esseva trovate un manco general de aeration, e le alveolos esseva plenate de liquido edematose, erythrocytos, e massas de macrophagos cargate de hemosiderina. Tincturationes a ferro esseva confirmatori.

Es revistate le question del symptomatologia e del pathogenese de hemosiderosis pulmonar e etiam le varie existente theorias etiologic relative a ille condition. Le diagnose es discutite. Es sublineate le importantia del complexo clinic de symptomatos

respiratori con hemoptysis e sever anemia a carentia de ferro que frecuentemente manifesta aspectos hemolytic. Es exprime le spero que in tanto que le membros del profession medical deveni de plus in plus conscie del existentia de iste entitate, illo es recognoscite plus precocemente, de maniera que le opportunitates de studiar lo deveni plus frequente.

## BIBLIOGRAPHY

1. Waldenström, J.: Relapsing, diffuse, pulmonary bleedings or hemosiderosis pulmonale, *Acta radiol.* **25**: 149, 1944.
2. Wyllie, W. G., Sheldon, W., Bodian, M., and Barlow, A.: Idiopathic pulmonary haemosiderosis (essential brown induration of the lungs), *Quart. J. Med.* **17**: 25, 1948.
3. Browning, J. R., and Houghton, J. D.: Idiopathic pulmonary hemosiderosis, *Am. J. Med.* **20**: 374, 1956.
4. Soergel, K. H.: Idiopathic pulmonary hemosiderosis: review and report of two cases, *Pediatrics* **19**: 1101, 1957.
5. Fleischner, F. G., and Berenberg, A. L.: Idiopathic pulmonary hemosiderosis, *Radiology* **62**: 522, 1954.
6. Smith, W. E., and Fienberg, R.: Early nonrecurrent idiopathic pulmonary hemosiderosis in an adult. Report of a case, *New England J. Med.* **259**: 808, 1958.
7. Hutchison, H. E.: Essential pulmonary haemosiderosis: report of a case with description of histological findings, *Glasgow M. J.* **35**: 217, 1954.
8. Blachford, R. D.: Idiopathic pulmonary haemosiderosis: report of a case, *Guy's Hosp. Rep.* **103**: 26, 1954.
9. Nancekivell, L.: Acute idiopathic pulmonary haemosiderosis, *Brit. M. J.* **1**: 431, 1949.
10. Steiner, B.: Essential pulmonary haemosiderosis as an immunohaematologic problem, *Arch. Dis. Childhood* **29**: 391, 1954.
11. Boros-Nachtnebel, O., cited by Wyllie et al.<sup>2</sup>
12. Wigod, M.: Idiopathic pulmonary hemosiderosis: report of a case in early childhood with severe anemia, *New England J. Med.* **253**: 413, 1955.
13. Gellis, S. S., Reinhold, J. L. D., and Green, S.: The use of aspiration lung puncture in the diagnosis of idiopathic pulmonary hemosiderosis, *Am. J. Dis. Child.* **85**: 303, 1953.
14. Irwin, J. M., and Snowden, P. W.: Idiopathic pulmonary hemosiderosis: report of a case with apparent remission from cortisone, *J. Dis. Child.* **93**: 182, 1957.
15. Jonsson, B., Vahlquist, B., and Agren, K.: Essential pulmonary hemosiderosis: case report, *Blood* **6**: 665, 1951.

## RECURRENT ATTACKS OF GENERAL PARESIS AFTER 12 AND 18 YEARS \*

By C. W. BARNETT, M.D., F.A.C.P., *San Francisco, California*

IN 1942 Dattner and Thomas<sup>1</sup> pointed out that the most important indication of activity in neurosyphilis is the cell count in the spinal fluid. They believe that there is always a pleocytosis in progressive infections, and that a normal white count is good evidence of inactivity. Positive serologic tests or abnormal

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From the Department of Medicine, Stanford University School of Medicine, San Francisco.

Requests for reprints should be addressed to C. W. Barnett, M.D., Professor of Medicine, Stanford University School of Medicine, 300 Pasteur Dr., Palo Alto, California.

colloidal gold curves may persist for years in completely quiescent infections and may be disregarded. An elevated protein is of some significance, but is less important than the cell count. The outcome of treatment is considered to be entirely satisfactory if the cell count is normal and the protein normal or slightly high, no matter what the serologic tests and gold curve show. This type of spinal fluid is generally referred to as the Dattner-Thomas type.

Since their report, this concept of the evaluation of activity in neurosyphilis has been widely accepted, and treatment is not continued or repeated until complete negativity is attained, as was commonly done before. At times, the arrest may be temporary, and an active type of spinal fluid may reappear and be followed by a clinical exacerbation. Thomas<sup>2</sup> believes, however, that this will occur very soon after treatment, usually within a year, and he reports that such a relapse has never been seen at Bellevue Hospital more than 15 months after treatment. This is a good working rule but it is not infallible, and the following case is presented because two such clinical and serologic relapses occurred over a total period of almost 20 years.

#### CASE REPORT

A white American housewife of 36 was first seen on August 30, 1941, when she complained of nervousness. She had been married in 1924, and three months later a skin eruption developed and her hair fell out. She was given about 10 intravenous injections for "eczema" and the symptoms went away.

In 1930 the patient became nervous and was slightly confused at times, and her ability to work as a bookkeeper was impaired. The blood Wassermann was found to be positive, and she was given three courses of intravenous and intramuscular injections, lasting about four months each and separated by rest periods of from four to five months. Her symptoms disappeared.

In 1936 the patient consulted a physician for a re-evaluation and was found to have a positive blood and spinal fluid, although she was asymptomatic at the time. She was treated for a year, after which the spinal fluid was negative. Therapy was continued for an additional six months. She did not remember the details of this treatment, except that it consisted of both intravenous and intramuscular injections.

In 1940 the patient became quite nervous but blamed this on some emotional difficulties. In January, 1941, she consulted another doctor because she was worried about syphilis, and was found to have a positive Wassermann. She was given one intravenous and one intramuscular injection weekly, with some relief, until the time she was admitted to hospital in August.

On physical examination the patient was quite thin and extremely nervous, with great hyperactivity of all deep reflexes and bilateral positive Hoffmann's signs. There were no other significant abnormalities. The cerebrospinal fluid showed 12 white blood cells per cubic millimeter, a positive Pandy's test, and a colloidal gold curve of 5554300000; a Kolmer-Wassermann was 44000.

A diagnosis of incipient paresis was made, and the patient was treated with weekly injections of Iodobismitol and tryparsamide. She developed visual disturbances after the second tryparsamide injection, so this drug was discontinued and was replaced by Aldarsone, which she was able to take without reaction. Treatment was continued until September, 1942, when she moved away. During this time she received 29 injections of Iodobismitol, two of tryparsamide, and 41 of Aldarsone. The spinal fluid on April 21, 1942, showed 5 cells, a negative Pandy's test, a gold curve of 1122210000, and a 44000 Kolmer.

The patient continued treatment for another year elsewhere, and then had another



six months of therapy after a lapse of a year. On October 27, 1944, she returned for a re-examination. She was feeling well and had gained some weight. Physical examination was negative except for hyperactive reflexes. The spinal fluid showed 2 cells, 20 mg. of protein per 100 ml., a colloidal gold curve of 0000000000, and a negative Kolmer. She was advised to discontinue treatment and to return in six months, which she did not do.

On November 9, 1948, the patient returned with a story of having been perfectly well until six months before. In February, 1947, she had had a negative spinal fluid. Her symptoms were increasing nervousness and progressive loss of weight (from 138 to 114 pounds). She had become emotionally unstable and had noted a loss of memory. She had stopped working, but the symptoms had progressed. Again there was nothing on physical examination except the greatly hyperactive reflexes and positive Hoffmann's signs. The clinical impression was that she was again suffering from early paresis, and this diagnosis was confirmed by a spinal fluid examination which showed 35 lymphocytes per cubic millimeter, a strongly positive Nonne's test, a colloidal gold curve of 5555543210, and a 4440 Wassermann. The blood count and urinalysis were normal. Fluoroscopic examination of the chest showed no evidence of aortitis.

TABLE 1  
A Summary of Spinal Fluid Examinations

Date	Cells/cu. mm.	Protein	Coll. Gold	Kolmer
8/30/41	12	Increased	5554300000	4400
4/21/42	5	Normal	1122210000	4400
10/27/44	2	20 mg. per 100 ml.	0000000000	0000
11/8/48*	35	Increased	5555543210	4440
3/5/49	0	Normal	4444322100	4100
9/28/49	0	Normal	4333321000	0000
6/13/50	0	Normal	1223321000	0000
9/21/51	0	Normal	1122110000	0000
4/13/54	2	Normal	1122321100	0000
9/23/58	0	Normal	1112110000	0000

\* Penicillin and fever therapy were given at this time.

The patient was hospitalized and was given crystalline penicillin G in doses of 100,000 units every three hours for 120 doses, a total of 12 million units. In addition, fever therapy was induced by intravenous typhoid vaccine. She had seven bouts of fever, with a total of 13 hours over 40° C.

The nervousness improved gradually after this treatment until by September, 1951, the patient was feeling better than she had in many years. She returned for periodic physical examinations, which showed nothing but hyperactive reflexes. Her last visit was in September, 1958, when she came in because of eczema of the hands, but she was otherwise well.

The results of her spinal fluid examinations are shown in table 1.

#### DISCUSSION

This patient demonstrates the importance of part of the Dattner-Thomas concept of spinal fluid interpretation, in that each of the two observed relapses was accompanied by spinal fluid recurrences that included pleocytosis. What makes this case most unusual is the long periods of time that elapsed between the recurrences. I am quite sure that the second relapse that I observed was

early paresis, and I believe the first one was too. From the history, I also believe that the initial attack in 1930 was probably incipient paresis, and that this patient has had three paretic episodes with 12- and six-year intervals between attacks, a most unusual series of events.

Although most neurologic recurrences take place within a year after treatment has been stopped, this case demonstrates that this is not always so, and that no definite interval can be chosen beyond which progression of this type cannot occur.

#### SUMMARY

A case is presented in which three separate attacks of early paresis occurred with periods of 12 and six years between attacks. The first two episodes were treated with metal chemotherapy and the last with penicillin and fever therapy, which has resulted in a 10-year cure. It is pointed out that the Dattner-Thomas concept of reactivation of the cerebrospinal fluid when a clinical progression occurs is borne out in this case, but the belief that such progressions will always occur within a year of treatment is manifestly untrue.

#### SUMMARY IN INTERLINGUA

Dattner e Thomas ha proponite considerar therapia pro neurosyphilis efficace e adequate si le numeration de cellulas e le determination del contento de proteina in le liquido cerebrospinal ha retornate al normas, mesmo si le tests serologic pro syphilis e le curva de auro colloidal remane anormal. Ille autores asseri in plus si un progresso clinic occorre post le tractamento, illo es precedite per pleocytose e que isto occorre quasi semper intra un anno post le tractamento. Iste conceptiones es extensamente acceptate.

Un femina de racia blanc de 36 annos de etate esseva primo vidite le 30 de agosto 1941, con le gravamine de extreme nervositate. Illa habeva disveloppate un eruption cutanee e alopecia tres menses post su maritage in 1924 e habeva recipite 10 injectiones intravenose con le resultado de un restablimento immediate.

In 1930 le patiente deveniva nervose e confuse e esseva tractate durante plus que un anno con injectiones intravenose e intramuscular, resultante in le alleviamento del symptommas.

In 1936, un examine routinari revelava un positive test serologic pro syphilis in le sanguine e le liquido spinal, e le patiente esseva tractate de novo durante plus que un anno usque le test del liquido spinal esseva negative.

In 1940 illa deveniva nervose e esseva tractate ab januario ad agosto 1941 (a qual tempore le autor la videva) con chimotherapie metallic.

In le examine physic illa esseva magre e multo nervose. Le reflexos profunde esseva hyperactive. Le signos de Hoffmann esseva positive. Le liquido cerebrospinal monstrava 12 leucocytos per  $\text{mm}^3$ , positivitate del test de Pandy, un curva de auro colloidal de 5554300000, e un test de Kolmer-Wassermann de 44000.

Esseva facite le diagnose de paresis incipiente. Chimotherapie metallic esseva initiate e mantenite durante tres annos. Al fin de iste periodo le patiente se trovava ben e le liquido cerebrospinal esseva negative.

Le 9 de novembre 1948, le patiente retornava con le reporto de crescente grados de nervositate e un progressive perdita de peso durante le passate sex menses. Illa esseva emotionalmente instabile. Su memoria comenciava devenir infidel. Su reflexos profunde esseva de novo hyperactive. Le signos de Hoffmann esseva de novo positive. Esseva facite le diagnose de recurrente paresis, e isto esseva confirmate per le constatacion de 35 lymphocytos per  $\text{mm}^3$  de liquido cerebrospinal, insimul con forte posi-

tivitate del test de Nonne, un curva de auro de 5555543210, e un test de Kolmer-Wassermann de 4440.

Le patiente esseva tractate con penicillina e therapia pro febre. Illa se restabliva clinicamente e ha continuate trovar se ben usque al tempore de su plus recente examine le 23 de septembre 1958. Le liquido cerebrospinal esseva normal le 28 de septembre 1949 e ha remanite normal depost.

Le recurrentias clinic in iste caso esseva accompagnate de recurrentias in le liquido cerebrospinal, incluse le presentia de pleocytosis, sed le intervallos de tempore inter iste episodios esseva inusualmente longe.

#### BIBLIOGRAPHY

1. Dattner, B., and Thomas, E. W.: The management of neurosyphilis, Am. J. Syph., Gonorr. and Ven. Dis. **26**: 21, 1942.
2. Thomas, E. W.: Syphilis: its course and management, 1949, The Macmillan Company, New York, p. 239.

### USE OF CORTICOSTEROIDS IN STOKES-ADAMS SYNDROME \*

By EDWARD L. PERRY, M.D., *La Crosse, Wisconsin*, and JAMES L. JAECK, M.D., *Sheboygan, Wisconsin*

THIS case is presented to demonstrate that treatment with cortisone was probably effective in bringing about cessation of syncopal and convulsive attacks associated with heart block after other measures had failed.

The history of this type of disorder is very completely covered in Major's *Classic Description of Disease*.<sup>1</sup> The first case of this type was described by Morgagni in 1776. He described an attack of "epilepsy" occurring in a 68 year old priest, during which the pulse became slow. The author felt that the cause of this attack was in the heart rather than in the brain. Robert Adams in 1827 reported another case of a man 68 years of age who had experienced 20 attacks of syncope over a seven-year period. He had a pulse rate of 30. William Stokes in 1846 reviewed the previously published cases and added his own. Two other early physicians also reported cases—Thomas Spens in 1793 and Sir William Burnett in 1824. Since the time of Stokes the syndrome under discussion has been variously known as the Morgagni-Adams-Stokes, the Adams-Stokes or the Stokes-Adams syndrome.

Stokes-Adams syndrome has been defined by De Boer<sup>2</sup> as "every disturbance of the action of the heart that begins and ends abruptly and causes such interruption of the circulation that more or less complete cerebral ischemia results." This definition includes patients with some degree of heart block between

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From the Departments of Internal Medicine and Pathology, The Gunderson Clinic, and La Crosse Lutheran Hospital, La Crosse, Wisconsin.

Requests for reprints should be addressed to Edward L. Perry, M.D., 1836 South Avenue, La Crosse, Wisconsin.

attacks, those with arrhythmias without any heart block between attacks, and those with arrhythmias without any heart block between the episodes of unconsciousness or convulsions. Since 1927 it has been recognized that the attacks may be brought on by a variety of circumstances. Parkinson et al.<sup>8</sup> separated patients with Stokes-Adams episodes into the following four categories: group 1, ventricular standstill alone, 33 cases; group 2, ventricular tachycardia followed by ventricular standstill, 18 cases; group 3, ventricular tachycardia or ventricular fibrillation, or both, without ventricular standstill, 13 cases; group 4, extreme bradycardia with complete heart block, two cases. In their experience, patients with ventricular standstill had a better prognosis than did those with ventricular tachycardia or ventricular fibrillation. Others have also described this syndrome as being due to several types of cardiac arrhythmia, including those mentioned above,<sup>4, 5, 6, 7</sup> as well as simultaneous auricular and ventricular standstill<sup>8</sup> and paroxysmal ventricular standstill.<sup>9</sup> The mechanism is ordinarily circulatory, due to coronary atherosclerosis, either with or without actual myocardial infarction.<sup>10, 11</sup> According to Hurst,<sup>5</sup> these attacks may also occur in cases of calcific aortic stenosis and in diphtheria and

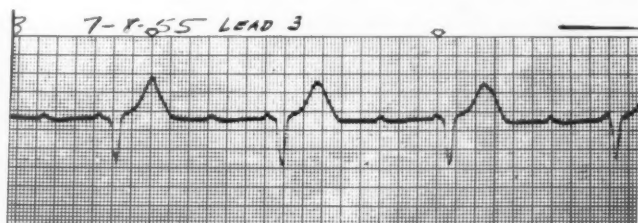


FIG. 1. Initial electrocardiogram showing complete heart block.

rheumatic fever, although in these, actual syncope is rare. Various degrees of A-V block may also be produced by digitalis and by quinidine. The actual unconsciousness is due to cerebral ischemia, and there may be all grades of disturbance, from dizziness to a major convulsive episode.<sup>12</sup> Before the onset of ventricular fibrillation there is usually a change in the ventricular rate, with premature beats and groups of fibrillary waves.<sup>13</sup>

#### CASE REPORT

A 66 year old female was admitted to the La Crosse Lutheran Hospital on July 8, 1955. In March, 1955, she had been found to have hypertension. She was given some pills, probably digitalis, but after about three weeks she became very nauseated and short of breath. She was hospitalized for eight weeks, during which time she had her first episode of unconsciousness. Despite the use of various medications, including isoproterenol, she had had no relief; on the contrary, the attacks had become more frequent, and at the time of admission to this hospital had been occurring eight or 10 times daily. At times the periods of consciousness lasted up to one hour. Before these attacks there was a premonitory period during which there were faintness and a hard pounding of the heart. The patient would also feel pressure in the throat and in the upper substernal region, and numbness in the hands and lips. The attacks would come on at any time of the day, and were unrelated to exertion.

On examination, the patient was well nourished but pale. The blood pressure was 180/75 mm. of Hg. The heart was enlarged to the left anterior axillary line. The pulse was slow, with a rate of about 40, with regular rhythm but punctuated at times by extrasystoles. The lung fields were clear. The liver was not enlarged, and the rest of the physical examination, including neurologic examination, was negative. During attacks of syncope there were cyanosis, extreme restlessness and, at times, grunting, irregular respirations. The white blood cell count was

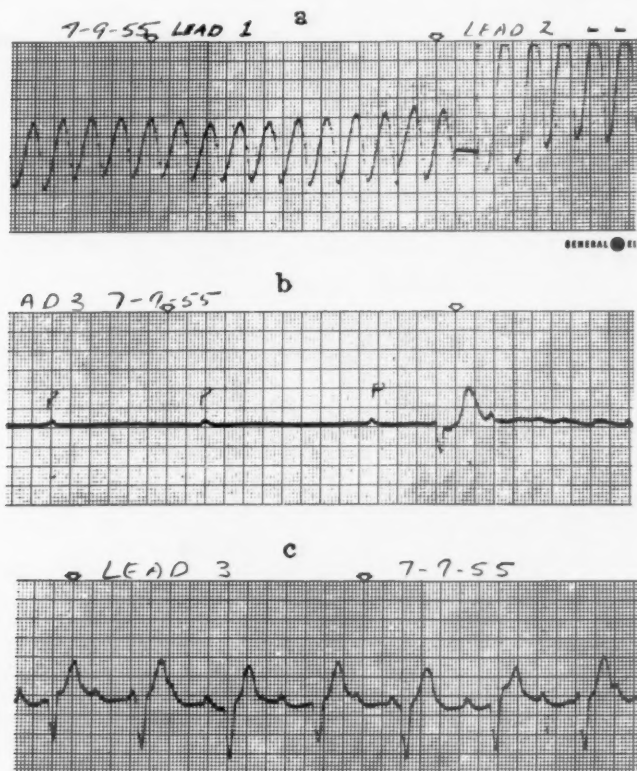


FIG. 2. Electrocardiogram taken during Stokes-Adams attack, demonstrating (a) ventricular tachycardia, (b) prolonged period of ventricular asystole, and (c) complete A-V block with ventricular rate of 66 after recovery from attack.

15,200; hemoglobin, 12.3 gm.; red blood count, 4,300,000. Urinalysis showed 3 plus albumin but was otherwise normal. A blood sedimentation rate was 18 mm. in one hour (Westergren). The blood serologic test for syphilis was negative. Blood urea nitrogen, 17 mg.%. X-ray of the chest showed marked cardiac enlargement; the aorta was wide and tortuous; congestive changes were present in the lung bases. The initial electrocardiogram showed complete auriculoventricular block, with an auricular rate of 100 to 110 per minute; the ventricular rate was 34 and regular. Frequent multifocal ventricular ectopic beats were also noted. The day following

admission an electrocardiogram was obtained while the patient was in one of her convulsive episodes. This initially revealed ventricular tachycardia with a rate of 210. Only a few ventricular contractions were seen, occurring infrequently and irregularly. There followed a period of 12 seconds of ventricular asystole, then a few ventricular complexes, and then asystole again for 27 seconds. Then the ventricles began contracting again from multiple foci at a rate of 45, with an auricular rate of 140 per minute. The rate then became more rapid from a single focus, but still with complete A-V block.

Treatment initially consisted of ephedrine, amobarbital, aminophylline and epinephrine. Because of the presence of fever of undetermined etiology and leukocytosis, the patient was also given tetracycline. Pentaerythritol tetranitrate was used to try to improve the coronary blood flow. On July 11 the patient had one attack

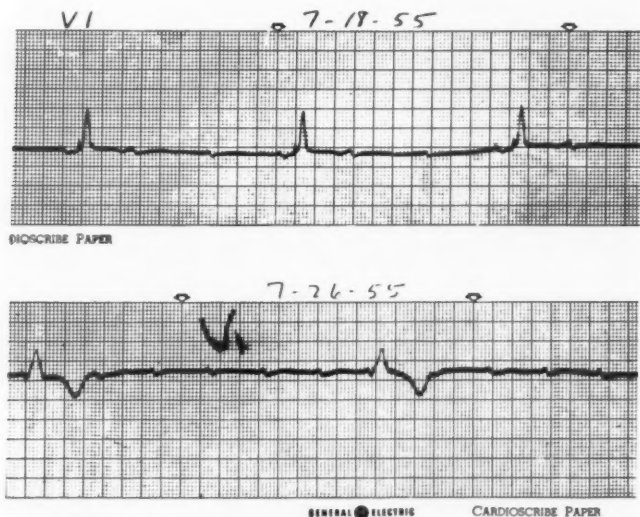


FIG. 3. A (above). Three-to-one A-V block with right bundle branch block during cortisone therapy. B (below). Complete A-V block with ventricular rate of 13 following cessation of cortisone treatment.

of unconsciousness lasting about three hours, during which she was very restless, with irregular breathing and, at times, cyanosis. On this date cortisone was started in a dosage of 25 mg. every six hours. She was also given potassium chloride and diphenylhydantoin. The following day she had another very prolonged attack, and then was completely free of episodes until July 26, the day of her death. On July 18, one week after cortisone treatment was begun, an electrocardiogram showed 3-to-1 second degree heart block. The cortisone was reduced because it was felt it might be aggravating her cardiac decompensation, until on July 20 she was receiving only 12½ mg. every 12 hours. On July 23 the cortisone was stopped entirely. Other medications were continued. On July 26 the patient had three more attacks of Stokes-Adams syncope with slight convulsions. The blood pressure at that time was 190/40 mm. of Hg; pulse rate, 13. Later that same evening she vomited several times and perspired profusely. The pulse rate at that time was 11 per minute.



An electrocardiogram again showed complete A-V block. The patient was treated with both ephedrine and epinephrine, but neither had beneficial effect, and she died that evening.

At autopsy the heart weighed 510 gm. There was hypertrophy of the walls of both the right and left ventricles. The mitral valve measured 6.0 cm. in circumference and showed marked scarring and retraction of its leaflets. The chordae tendineae were notably shortened, and some fusion was present. There was also some nodular thickening of the mitral leaflets and ring, and there seemed to be



FIG. 4. Photomicrograph ( $\times 150$ ) showing perivascular scar in myocardium, considered to be residual of rheumatic fever.

calcium deposit in both the valve and the valve ring. On the floor of the right atrium, and extending onto the septal cusp of the tricuspid valve, there was a conspicuous subendocardial scar. The coronary arteries were widely patent and soft, and showed very little narrowing of the lumen and no evidence of thrombosis.

Microscopically there were fibrosis and calcium deposition in the leaflets of the mitral valve. No vegetations were present. There was some vascularization but very little cellularity. This was interpreted as being the result of healed or inactive rheumatic valvulitis. One section from the myocardium showed an intramural small artery in the myocardium of the left ventricle, with the lumen attenuated due to a concentric perivascular scar. In another region there was a focal cellular infiltrate

of plasma cells, lymphocytes and monocytes, fairly typical of the so-called diffuse interstitial myocarditis of rheumatic heart disease. No typical Aschoff bodies were present, however.

In a section taken from the region of the origin of the bundle of His, beginning at the A-V node, a round structure was found that was outlined by a rim of calcium which, on higher magnification, was seen to be a heterotopic nodule of bone marrow.

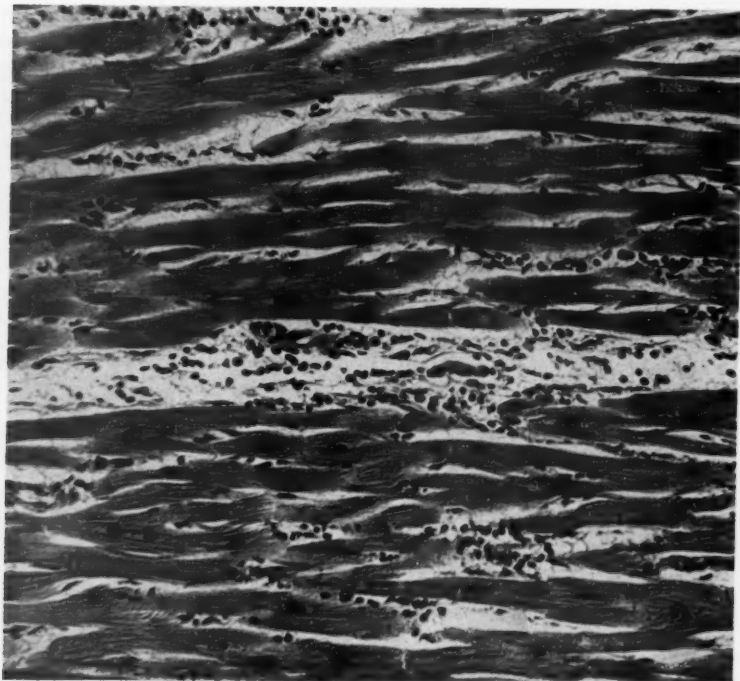


FIG. 5. Photomicrograph ( $\times 150$ ) of diffuse interstitial myocarditis. No Aschoff bodies. Rheumatic myocarditis?

#### DISCUSSION

*I. Treatment: Common Methods and New Developments:* Current methods of treatment in Stokes-Adams syndrome include the drugs ephedrine, epinephrine, isopropyl nor-epinephrine (isoproterenol, or IPN) and atropine.<sup>5, 7, 8, 14, 15, 16</sup> The latter is used particularly in cases of hypersensitive carotid sinus with cardiac arrest and syncope. Barium previously found quite frequent usage, but more recently has been largely abandoned.<sup>14</sup> Both quinidine and procaine amide would theoretically be ideal for prevention of ventricular tachycardia or fibrillation, but many instances of undesirable and even dangerous effects of these drugs have been reported, particularly in the presence of A-V block or

bundle branch block.<sup>15</sup> Some authors have reported precipitation of attacks of ventricular tachycardia or fibrillation with the use of these drugs.<sup>17, 18</sup> Robbin<sup>16</sup> and his group and Schumacher and Schmock<sup>19</sup> feel that isoproterenol is the drug of choice in this syndrome. It causes an increase both in the cardiac rate and in the amplitude of the myocardial contraction. It also results in an increase in stroke volume and in coronary artery flow. Robbin and his group feel that IPN has a stimulating effect on the active ventricular pacemaker of the heart and still does not have the tendency to incite lower ventricular foci.



FIG. 6. Photomicrograph ( $\times 75$ ) of subendocardial nodule in bundle of His almost at A-V node. Note calcification at periphery of nodule and hematopoietic bone marrow in its center.

IPN is used sublingually, and may also be used intravenously in an emergency. Zoll et al.,<sup>18</sup> however, have recently stated that isoproterenol still has not established a place in the therapy of Stokes-Adams attacks. They believe that, for a slow idioventricular rhythm or standstill, ephedrine and epinephrine are still the best drugs. The latter authors have also employed the external electrical pacemaker, which has been very effective in several instances in repeatedly terminating ventricular standstill and in maintaining an adequate heart rate for hours or days at a time. They have also introduced an electrical shocking defibrillator, which is used in cases of ventricular tachycardia or fibrillation before the electrical pacemaker is brought into action.

Chandler and Rosenbaum<sup>20</sup> have recently reported a case of Adams-Stokes

syndrome where it was necessary to use intravenous isoproterenol and the electric artificial pacemaker simultaneously to maintain adequate heart action.

McLemore and Levine<sup>21</sup> in 1955 also proposed cholecystectomy as of possible therapeutic value in patients with Stokes-Adams syndrome and with a diseased gall-bladder. They performed cholecystectomies on seven patients, five of whom had complete heart block, and felt that the number of episodes was definitely decreased postoperatively.

In a subsequent report Vandam and McLemore<sup>22</sup> reported circulatory and respiratory arrest in six of 22 patients with heart block undergoing surgery. They felt that factors of great importance were the anesthesia and also the reflexes from the trachea and upper abdominal organs, and the gall-bladder region in particular. They recommended that the following measures be taken or prepared for in the case of any patient with heart block undergoing surgery: (a) epinephrine readily available for intramuscular or intravenous use; (b) an intravenous infusion of isoproterenol readily available; (c) molar sodium lactate (see below); (d) atropine to block the vagus; (e) a barbiturate to be used preoperatively, but no opiates to be given; (f) local anesthesia only to be employed whenever possible; (g) an electrocardiographic monitor applied and used continuously; (h) artificial pacemaker applied before surgery; (i) various external stimuli, such as slapping the chest, pricking the heart with a needle, massage through the diaphragm, etc., to be tried in emergency before thoracotomy and manual systole are resorted to.

Bellet<sup>14, 23, 24</sup> has recently pointed out the value of molar sodium lactate in the prevention and treatment of Stokes-Adams syndrome. It has been used especially in association with cardiac arrest, and is most effective when given very promptly. Forty to 80 c.c. intravenously may be given rapidly, and as much as 1 L. in six hours has been injected. This solution has also been used by intracardiac injection, and has been successful when used in this manner after intravenous infusion has failed. Untoward effects noted with this treatment have been the production of ventricular extrasystoles and ventricular tachycardia.<sup>25</sup>

*II. Use of Corticosteroids in Heart Block:* The rationale for the use of cortisone in this patient was the possibility that her heart block might be associated with inflammatory exudate and edema secondary to rheumatic myocarditis. Prinzmetal and Kenamer<sup>11</sup> reported a case of ventricular asystole with syncope due to complete heart block following posterior myocardial infarction, which was terminated on two distinct occasions by the use of ACTH. Another case has recently been reported<sup>26</sup> where complete heart block occurred after an anterior myocardial infarction. This was abolished, and the pulse rate increased from 30 to 88 in a one-hour period after 100 mg. of cortisone were given intramuscularly. In both of these cases it was felt that the anti-inflammatory effect was responsible for the improvement.

In a study of patients with rheumatic fever, Massell<sup>27, 28</sup> found that 54 of 66 patients showed a reversion to normal of a previously prolonged PR interval during treatment with corticosteroid hormones. Another very interesting report was made by Lown and his group<sup>29</sup> in 1955. They found distinctly short PR intervals occurring in patients with Cushing's syndrome, whereas in patients with Addison's disease the PR interval tended to be longer, and there were

several cases of heart block. The A-V conduction time correlated closely with the urinary 17-ketosteroid excretion, and also with the finding of adrenal cortical hyperplasia at surgery. This group felt that the C-11-oxysteroids coöperated biologically with the sympathetic nervous system in the regulation of A-V conduction.

Alkalosis may also be a very important factor. This has been postulated as the cause of the beneficial effect of molar sodium lactate by Bellet<sup>23, 24</sup> and by Vandam and McLemore.<sup>22</sup> It is well known that both cortisone and ACTH tend to produce a metabolic alkalosis. Houle and his group<sup>30</sup> found a diminished cardiac and pressor response to epinephrine when acidosis was present. In experiments with dogs, Price and Helrich<sup>31</sup> found that lowering the pH of the blood depressed myocardial contractility to a marked degree, and that the acidosis was frequently associated with spontaneous failure of the heart. Previous descriptions of the electrocardiographic effects of alkalosis have not mentioned the effect on the conduction time, but rather the lowering of the T waves, prolongation of the QT interval and the production of extrasystoles.<sup>32</sup>

*III. Nodules in the Conduction System of the Heart:* One other very interesting aspect of this case was the nodule containing bone marrow present within the conduction system of the heart. Yater and Cornell<sup>33</sup> in 1935 reported on nine cases with a calcareous or fibrocalcareous lesion of the bundle of His. These indicated that the bundle of His may be seriously damaged and still function quite normally from time to time. Apparently only a few strands of conduction tissue are necessary to prevent permanent, complete heart block. The case under discussion is the first, however, where heterotopic bone marrow has been reported in the conduction system. Apparently this was not completely obstructing, since while receiving cortisone this patient showed reversion from third degree to second degree heart block.

#### SUMMARY AND CONCLUSIONS

1. A case of Stokes-Adams syndrome is presented that clinically exhibited both ventricular tachycardia and ventricular standstill as the basis for the syncopal and convulsive episodes. This patient had been unresponsive to the usual methods of treatment of this syndrome.

2. With institution of cortisone treatment the degree of heart block changed from complete to second degree (3:1), and with withdrawal of cortisone there was again reversion to complete A-V block, with a progressively slowing pulse rate and death.

3. The beneficial effect of cortisone in this case was felt to be real, and based upon either (a) the anti-inflammatory effect of the medication upon the rheumatic or inflammatory lesions in the conduction system, or (b) the production of a metabolic alkalosis.

4. The use of other drugs and methods in treatment of Stokes-Adams disease is discussed.

5. An interesting pathologic finding in this case was the presence of a calcified nodule containing bone marrow, present in the conduction system in the region of the A-V node. This was not completely obstructing to the conduction tissue, since clinically there was a change from complete to second degree A-V block despite its presence.

## SUMMARIO IN INTERLINGUA

Es presentate un caso de syndrome de Stokes-Adams in un patiente feminin de 66 annos de etate. Illa habeva habite episodios de syncope, occurrente octo a 10 vices per die, de durationes de usque a un hora. Le electrocardiogramma monstrava un complete bloco atrio-ventricular, con un frequentia ventricular de 34 per minuta. Durante le episodios de syncope o convulsion, provas electrocardiographic esseva obtenite pro periodos de asystole ventricular e etiam pro intervallos de tachycardia ventricular. Tractamentos con ephedrina, aminophyllina, a epinephrina habeva remanite sin effecto. Alora un tractamento con cortisona esseva initiate, in un dosage de 25 mg omne sex horas, e pro duo septimanas le patiente remaneva completamente libere de attaccos. Un septimana post le initiation del tractamento a cortisona, un electrocardiogramma monstrava 3 a 1 in le bloco atrio-ventricular del secunde grado. Tres dies post le suspension del cortisona, le attaccos syncopie de Stokes-Adams e le complete bloco atrio-ventricular recurreva. Le frequentia ventricular deveniva 13 per minuta, resultante in le morte del patiente.

In recente tempores, multe expertos ha opinare que norepinephrina isopropyllic es le droga de election in le tractamento de attaccos de Stokes-Adams, sin riguardo a si lor causa es asystole ventricular o tachycardia ventricular. Recente reportos ha similimente signalate le beneficios effectuate per molar lactato de natrium e le uso de un centro externe e mechanic de rhythm-conduction.

Cortisona esseva usate in le presente patiente a causa del possibilitate que su bloco cardiac esseva associate con exsudato inflammatori e edema secundari a carditis rheumatic. Un altere e multo forte possibilitate es que alcalosis metabolic esseva producite, con melioration del conduction auriculo-ventricular.

Un constatacion inusual al necropsia esseva le presentia de un nodule de osso con medulla ossee in le region del nodo atrio-ventricular. Le necropsia revelava etiam plure lesiones reflectente un previe myocarditis rheumatic e fibrosis e calcification in le valvula mitral, indicante—probabilmente—un curate valvulitis rheumatic.

Le experientia de alteres in le uso de corticosteroides in casos del syndrome de Stokes-Adams es revistate. Nos opina que cortisona esseva probablemente benefical in le effectuation de un alleviamento temporari del attaccos de Stokes-Adams in iste patiente e que corticosteroides merita essayos clinic additional.

## BIBLIOGRAPHY

1. Major, R. H.: *Classic description of disease*, 1939, Charles C Thomas, Springfield, Illinois.
2. De Boer, S.: On the origin and essence of the Morgagni-Adams-Stokes syndrome, *Ann. Int. Med.* **37**: 48, 1952.
3. Parkinson, J., Papp, C., and Evans, W.: The electrocardiogram of the Stokes-Adams attack, *Brit. Heart J.* **3**: 17, 1941.
4. Robertson, E. S., and Mathews, A. C.: Paroxysmal ventricular fibrillation producing Adams-Stokes syndrome, *Arch. Int. Med.* **90**: 320, 1952.
5. Hurst, J. W.: Syncope due to cardiac arrhythmias, *Mod. Concepts Cardiovas. Dis.* **24**: 259, 1955.
6. Pastor, B. H., and Worrlow, S.: Electrocardiographic patterns in Stokes-Adams syndrome, *Ann. Int. Med.* **34**: 80, 1951.
7. Dupler, D. A.: Ventricular arrhythmia and Stokes-Adams syndrome. Report of case, *Circulation* **3**: 585, 1953.
8. Tuna, N., and Scott, J. W.: Stokes-Adams attacks with simultaneous auricular and ventricular standstill, *Circulation* **9**: 853, 1954.



9. Hick, F.: Paroxysmal ventricular standstill and its production by carotid sinus pressure, *Circulation* **9**: 857, 1954.
10. Phelps, M. B., and Lindsay, J. D., Jr.: Cortisone in Stokes-Adams disease secondary to myocardial infarction, report of case, *New England J. Med.* **256**: 204, 1957.
11. Prinzmetal, M., and Kenamer, M. D.: Emergency treatment of cardiac arrhythmias, *J. A. M. A.* **154**: 1049, 1954.
12. White, P. D.: Heart disease, 1951, The Macmillan Company, New York, p. 939.
13. Schwartz, S. P., quoted by Pastor and Worrlow.<sup>6</sup>
14. Bellet, S.: The treatment of Stokes-Adams seizures, *Mod. Concepts Cardiovas. Dis.* **26**: 393, 1957.
15. Robbin, S. R., Goldfein, S., Schwartz, M. J., and Dach, S.: The treatment of ventricular asystole, ventricular tachycardia and ventricular fibrillation associated with complete heart block, *Am. J. Med.* **18**: 577, 1955.
16. Larsen, W. E.: Complete block with Morgagni-Adams-Stokes syncope treated with large doses of epinephrine, case, *J. Kansas M. Soc.* **55**: 249, 1954.
17. Schwartz, S. P., Margolies, M. P., and Firenze, A.: Transient ventricular fibrillation. V. The effects of the oral administration of quinidine sulfate on patients with transient ventricular fibrillation during established A-V dissociation, *Am. Heart J.* **45**: 404, 1953.
18. Zoll, P. W., Linenthal, A. J., Norman, L. R., Paul, M. H., and Gibson, W.: External electric stimulation of the heart in cardiac arrest, *Arch. Int. Med.* **96**: 639, 1955.
19. Schumacher, E. E., Jr., and Schmock, C. L.: The control of certain cardiac arrhythmias by isopropyl nor-epinephrine, *Am. Heart J.* **48**: 933, 1954.
20. Chandler, D. E., and Rosenbaum, J. B.: Severe Adams-Stokes syndrome treated with Isuprel (isopropylarterenol) and artificial pacemaker, *Am. Heart J.* **49**: 295, 1955.
21. McLemore, G. A., and Levine, S. A.: The possible therapeutic value of cholecystectomy in Adams-Stokes disease, *Am. J. M. Sc.* **229**: 386, 1955.
22. Vandam, L. D., and McLemore, G. A.: Circulatory arrest in patients with complete heart block during anesthesia and surgery, *Ann. Int. Med.* **47**: 518, 1957.
23. Bellet, S., Wasserman, F., and Brody, J. I.: Molar sodium lactate. Its effect in complete auriculoventricular heart block and cardiac arrest occurring during Stokes-Adams seizures and in the terminal stage, *New England J. Med.* **253**: 891, 1955.
24. Bellet, G., Wasserman, F., and Brody, J. I.: Effect of molar sodium lactate in increasing cardiac rhythmicity, *J. A. M. A.* **160**: 1293, 1956.
25. Murray, J. F., and Boyer, S. H.: Ventricular arrhythmias after intravenous sodium lactate in heart block, *Circulation* **15**: 547, 1957.
26. Phelps, M. B., and Lindsay, J. D., Jr.: Cortisone in Stokes-Adams disease secondary to myocardial infarction. Report of a case, *New England J. Med.* **256**: 204, 1957.
27. Massell, B. F.: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis, *New England J. Med.* **251**: 183, 1954.
28. Massell, B. F.: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis, *New England J. Med.* **251**: 221, 1954.
29. Lown, B., Arons, W. L., Ganong, W. F., Vazifdar, J. P., and Levine, S. A.: Adrenal steroids and auriculoventricular conduction, *Am. Heart J.* **50**: 760, 1955.
30. Houle, D. B., quoted by Vandam and McLemore.<sup>22</sup>
31. Price, H. L., and Helrich, M.: The effect of cyclopropane, diethyl ether, nitrous oxide and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation, *J. Pharmacol. and Exper. Therap.* **115**: 206, 1955.
32. Barker, P. S., Schroder, E. L., and Ronzani, E.: The effects of alkalosis and of acidosis upon the human electrocardiogram, *Am. Heart J.* **17**: 169, 1939.
33. Yater, W. M., and Cornell, V. H.: Heart block due to calcareous lesions of the bundle of His; review and report of a case with detailed histopathologic study, *Ann. Int. Med.* **8**: 777, 1935.

## GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH PORPHYRINURIA\*

By RICHARD F. PINO, M.D., *Richmond Hill, N. Y.*

It is not too uncommon to find in the literature cases first diagnosed as Guillain-Barré syndrome that eventually prove to be porphyria. This contingency usually occurs when an alert observer notices the dark urine characteristic of porphyria, or when, in spite of a normally colored urine, the symptomatology makes one suspicious and, on examining the urine, one finds the pathognomonic porphyrins or precursors. Although in the case herein reported porphobilinogen and uroporphyrin were found in the urine after a diagnosis of acute infectious polyneuritis had been made, it is held that acute infectious polyneuritis was the primary diagnosis, with the abnormal porphyrins representing either a secondary change or a fortuitous finding.

### CASE REPORT

A 14 year old white female entered The Brooklyn Hospital for the first time on March 20, 1958, complaining of weakness in her legs. Three weeks prior to admission she had noticed a tingling sensation in her feet. Two weeks later she experienced the same sensation in her fingertips. This was followed by weakness in the legs. There was no recent history of upper respiratory infection or febrile illness. She had had an appendectomy in January, 1954. A suppurative appendix is alleged to have been found. A gastrointestinal series performed in 1956, because of a transient burning sensation in the abdomen following meals, revealed pylorospasm. Past history was otherwise insignificant.

On physical examination the temperature was 98.6° F.; pulse, 110; respiration, 20; blood pressure, 134/82 mm. of Hg. The only positive findings were neurologic. The cranial nerves were intact. There was bilateral decreased motor power in all movements at the shoulder girdle and in extension of the elbows. There was decreased power in flexion of the hips and knees, and in dorsiflexion of the ankles. The patient experienced difficulty in changing from a supine to a sitting position. Triceps, biceps, radial, patellar, ankle and abdominal reflexes could not be elicited on either side. There was no Babinski or Hoffmann sign. There was no muscular atrophy, nor were there any fasciculations. Pinprick was diminished over the fingertips and toes. Coördination was good.

Hemoglobin, hematocrit, white blood cell count, including differential, sedimentation rate and routine urinalysis were normal. Blood heterophil antibody determination was normal. Spinal fluid on admission was negative for white blood cells. Sugar and chloride were normal. The protein was elevated to 240 mg.%. Smear and culture were negative, as were spinal fluid Mazzini's and colloidal gold tests.

A diagnosis of Guillain-Barré syndrome was made and the patient was placed on prednisone, which was shortly changed to triamcinolone. The paralyses, however, increased in an ascending manner, involving more muscle groups of the lower and upper extremities, until the patient became quadriplegic. In addition, she developed

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From the Department of Medicine, The Brooklyn Hospital, affiliate hospital of State University of New York Down-state Medical College, Brooklyn, N. Y.

Requests for reprints should be addressed to Richard F. Pino, M.D., 107-43 124th Street, Richmond Hill, N. Y.

a right facial paresis, and her voice acquired a nasal quality. Swallowing became difficult, and respiration later became so labored that 20 days after admission a Drinker-Collins respirator was required. The vital capacity at this time was 20% of normal. Sensory nerve impairment became much more apparent. There was marked loss of position sense. Several transient episodes of urinary incontinence occurred. Whereas the weakness of the facial muscles and the difficulty in swallowing were of short duration, there was no return of any other muscle power for several weeks.

Twenty-seven days after admission, examination of the patient's urine revealed porphobilinogen, uroporphyrin and coproporphyrin. The urine, however, never turned to a port-wine color, even after exposure to the sun. Subsequent urine examinations throughout the patient's hospitalization revealed persistent porphyrinuria. Qualitative 24-hour urinary excretion studies for porphyrins were not made. The mother, maternal aunt, maternal grandmother and maternal grandfather of the patient showed no urinary porphyrins, nor was there a family history to suggest porphyria.

The following additional tests were performed, with nonsignificant results: chest, skull and abdominal x-rays, blood urea, blood sugar, serologic tests for viral and rickettsial diseases, examination for viral agents in the spinal fluid, spinal fluid lactic dehydrogenase, serum lead levels, total protein with A/G ratio, and serum cholesterol. A sedimentation rate five weeks after admission was 52 mm. in one hour. Repeated determinations for the hemoglobin, blood leukocyte and differential counts, as well as routine urinalyses, were all normal. A second colloidal gold test on the spinal fluid was 3322211100.

At the time the patient's paralyses were progressing, bilateral papilledema with hemorrhages and exudates developed. These were attended by photophobia. Spinal fluid pressure at this time was 490 mm. To relieve this pressure, lumbar punctures were performed every other day, 25 to 30 c.c. of spinal fluid being removed on each occasion. The taps were continued for about one month, after which time spinal puncture once a week proved to be adequate. The papilledema improved remarkably and eventually completely disappeared.

The spinal fluid protein had risen from an initial 240 mg.% to 434 mg.%, and had remained elevated throughout the hospital course. An occasional lymphocyte had been found in the spinal fluid; the greatest number, however, had been four cells per cubic millimeter. Spinal fluid cultures, including investigation for acid-fast bacilli, had repeatedly been sterile. Sugar and chloride determinations remained unremarkable. The fluid remained colorless and clear except for xanthochromia noted on one occasion. Repeated examinations of the spinal fluid for porphyrins proved negative.

The patient remained afebrile except for a short episode of mild temperature elevation associated with a thrombophlebitis of the left leg, which subsided with warm soaks and elevation. Blood pressure during hospitalization ranged between 150 and 120 systolic and 80 and 90 diastolic. The pulse remained at 120 during the initial period of hospitalization, but later, as the patient improved, it hovered about 100.

The vital capacity, which had dropped to a low of 5% of the predicted normal value, slowly increased, so that at the time of discharge it had reached 42% of normal.

With muscle power gradually returning, and need for respiratory aid markedly reduced, the patient was discharged on July 14, 1958, to the rehabilitation center of Goldwater Memorial Hospital. At the time of discharge she was able to flex and extend her neck. Muscle power in the scapular elevators was good, and slight motion had returned in the hands and hips, but none in the lower extremities.

Ability to cough and contract abdominal muscles remained poor. The cranial nerves persisted intact and the optic fundi were normal. Abdominal reflexes were still absent, as were the triceps, biceps, radial, patellar and ankle tendon reflexes. Position sense in the distal extremities was still poor. Vibratory sensation was absent in both upper and lower extremities, as well as at the iliac crests. It was present over the spinous processes down to the midlumbar level. Pinprick was slightly diminished from the hips down. It was decreased to absent bilaterally from the knees down, exclusive of the soles of the feet; it was intact elsewhere. Light touch was decreased to absent from the hips down. It was otherwise intact.

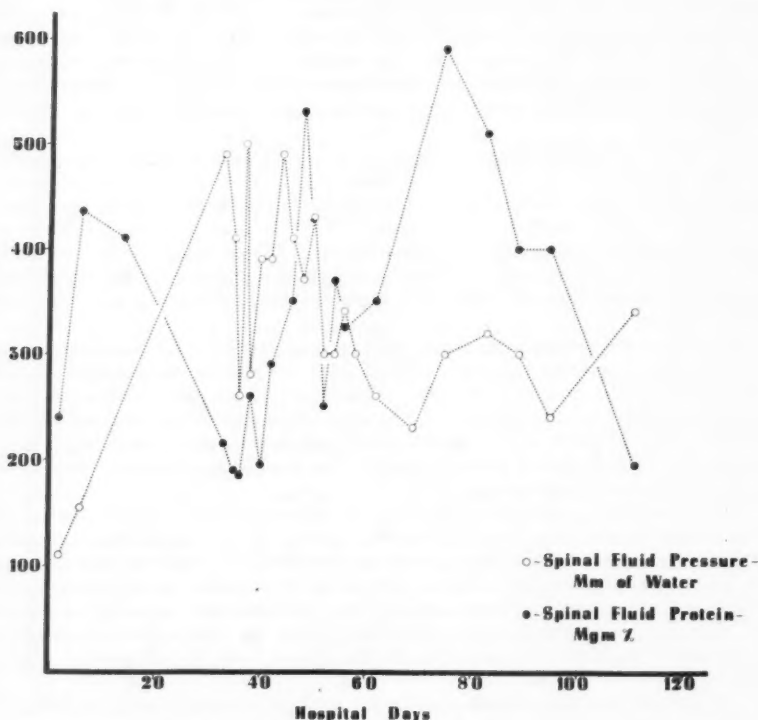


FIG. 1. Cerebrospinal fluid pressure and protein of lumbar punctures performed during hospitalization.

#### DISCUSSION

A diagnosis of Guillain-Barré syndrome rather than primary porphyria was made in view of the albuminocytologic dissociation of the spinal fluid, the papilledema, and the increased cerebrospinal fluid pressure, as well as the type of neuritis. In addition, there was nothing suggestive in the past or family history to indicate porphyria.

Although not essential, the demonstration of an increased cerebrospinal protein with little or no elevation of cells is an appreciable aid in the diagnosis

of the Guillain-Barré syndrome. Certainly this patient, with a protein content of from 186 to 590 mg.% in 25 lumbar punctures, and with cell counts ranging from zero to four lymphocytes per cubic millimeter, demonstrates typical albuminocytologic dissociation. The finding of urinary porphyrins in this patient prompted a review of the literature for reports of spinal fluid protein elevations in cases of porphyria. Lyons<sup>1</sup> reported a case of acute porphyria in a male who developed nuchal rigidity with a demonstrable Kernig's sign. Although two lumbar punctures disclosed clear fluid without organisms demonstrated on smear or culture, subsequent spinal fluid determinations suggested the presence of a meningitis, since there were an increased number of mononuclear cells (136 to 233/mm.<sup>3</sup>), increased opening pressure (240 to 600 mm. of water), and decreased sugar (56 to 50 mg.%). The one protein determination performed was 89.7 mg.%. In one patient Yeager<sup>2</sup> reported two protein determinations, 59 and 128 mg.%. Markovitz,<sup>3</sup> in a review of 69 cases of porphyria, discussed the spinal fluid changes in lumbar puncture performed in 24 of these patients. He reported the findings as normal in 17 and abnormal in seven cases, the abnormalities being minimal, consisting of the presence of from 5 to 10 cells, or a "mildly elevated protein." Hierons,<sup>4</sup> in his discussion of the pathology in five patients with porphyria, cited two cases of elevated cerebrospinal fluid protein, one at 65 mg.%, and the other at 130 mg.%. Freedman et al.<sup>5</sup> reported two cases, one with a protein of 55 mg.%, the other with a protein of 90 mg.%. Hare and Wilmore<sup>6</sup> disclosed one value of 51 mg.%. Petrie,<sup>7</sup> in three spinal fluid determinations performed on a patient, found readings of 70 and 50 mg.% of protein. Nesbitt<sup>8</sup> demonstrated proteins of 56 and 92.6 mg.% in one patient. Fisher<sup>9</sup> reported a protein of 65 mg.%. The only case of porphyria found in the literature where the spinal fluid protein was elevated to a degree comparable with this case was that of Avery,<sup>10</sup> who described an isolated xanthochromic spinal fluid with an opening pressure of 110 mm., 9 cells per cubic millimeter, and a total protein of 1,200 mg.%. Recognizing the unusually high protein, he entertained the possibility of a superimposed Guillain-Barré syndrome. The clinical course and past history of his patient, however, favored the diagnosis of porphyria.

It, therefore, may be stated that the great majority of patients with porphyria who have had cerebrospinal fluid protein determinations display a normal value, only a few manifesting mild hyperalbuminosis. The amount of cerebrospinal protein in the case herein presented was markedly elevated in multiple specimens taken over a period of months.

The severe papilledema reported in this patient was verified by many observers. It was associated with hemorrhages, exudates and photophobia. Although not a common finding, papilledema in the Guillain-Barré syndrome has been reported several times.<sup>11, 12</sup> It has, however, rarely been observed in porphyria. Barnes and Boshoff,<sup>13</sup> in their review of the ocular lesions in 84 patients with porphyria, observed that the discs were slightly blurred and hyperemic in two patients during acute attacks. One showed numerous hemorrhages, mostly in the vicinity of the discs. Other ocular lesions consisted of external and internal scarring of the lids, ectropion, blepharochalasis, symblepharon, hyaloid thickening of the conjunctiva, pemphigoid occlusion of the fornix, acute bullous conjunctivitis, and keratomalacic ulcers of the cornea and sclerae, resulting in dense scars and blindness. Periodic blindness has been

described in porphyria when no ocular lesions were apparent.<sup>14, 15</sup> This was thought to be a consequence of the toxic effects of the pigments on the cerebrum itself, although Waldenström feels that it may have been angiospastic in origin. Hierons<sup>4</sup> reports a case of bilateral papilledema in a 13 year old boy with porphyria, although the spinal fluid pressure was normal. In the vast majority of cases of porphyria, however, examination of the optic fundi has not revealed any pathologic changes.

The cause of the papilledema in Guillain-Barré syndrome is not completely known. It appears to be intimately related to the increased protein content of the spinal fluid, a possible explanation for which lies in increased production and decreased absorption. As for the former, it is thought that at the radicular level there is passage of an exudate through the walls of the dilated blood vessels, which, being in intimate contact with the spinal fluid, results in an increased protein level. On the other hand, congestion and edema of the nerve roots as they leave the intervertebral foramina cause obstruction, so that protein has lost one of its normal avenues for subsequent absorption. That such obstruction does occur has been adequately demonstrated by Biernacki,<sup>16</sup> who injected Thorotrast into the lumbar sac of a patient with Guillain-Barré syndrome. In favor of this theory are the comparative studies of Aring,<sup>17</sup> who found normal protein levels in fluid taken on cisternal puncture, whereas those fluids obtained from lumbar puncture showed considerably elevated protein. Bassoe<sup>18</sup> reported a case in which fluid taken from lumbar puncture and cisternal puncture demonstrated 2,000 and 25 mg.% of protein, respectively. It has been theorized that this excess protein in the spinal fluid mechanically plugs up the arachnoid villi (just as do cellular and fibrinous exudates), so that an external hydrocephalus is produced, with associated increased intracranial pressure and the resulting manifestation of papilledema. Joynt,<sup>11</sup> however, takes exception, inasmuch as in cases of Guillain-Barré syndrome where pneumoencephalograms have been made, no dilatation of the ventricular system has been demonstrated. He supports the theory that papilledema is due to cerebral edema. This he demonstrated both grossly and by biopsy at the time of a decompression procedure in a patient with Guillain-Barré syndrome.

The neuritis in the above case was partially manifested by an ascending paralysis. Although many authors claim that the neuritis of porphyria can manifest itself as a "Landry type of ascending paralysis," in Waldenström's own words, "This is an interesting example of a scientific cliché that is passed on from one author to another." He observed 100 patients with paresis, none of whom showed the typical ascent of the paralysis. The paralysis of porphyria may begin anywhere and progress unpredictably, being widespread simultaneously, or going from one muscle group to another. This fact is in keeping with the pathologic finding of patchy demyelination of the peripheral nerves and electrodiagnostic data<sup>20</sup> on skeletal muscle groups. Although respiratory paralysis is seen in both the Guillain-Barré syndrome and porphyria, facial nerve involvement such as this patient developed often accompanies the former. Whereas the patient's sensory disturbances were marked and objectively definite, sensory disturbances in porphyria are uncommon. Paresthesias do, however, occur. Waldenström states that only in cases where the symptoms had been of long duration had he been able to observe unequivocal diminution of superficial and deep sensibility.



Although it was felt that the presence of porphyrins in the urine of this patient was probably related to acute infectious polyneuritis, it should be clarified that the patient did not have "secondary porphyria." This term is commonly taken to mean a greater-than-normal amount of coproporphyrin in the urine. Coproporphyrin is found to be increased in various disease processes, e.g., coproporphyrin-I can be found in excessive amounts in acute febrile states, infectious hepatitis, obstructive jaundice, pernicious anemia, hemolytic anemia and leukemia; coproporphyrin-III is frequently found in greater amounts than normal in poliomyelitis, Hodgkin's disease, portal cirrhosis, aplastic anemia, and in metal or chemical poisoning.<sup>15</sup> Even uroporphyrin excreted in increased amounts has been found in association with the intake of chemicals (Sulfonal, Trional, Veronal) and with lead poisoning. In this patient, in addition to increased coproporphyrin and uroporphyrin, porphobilinogenuria was also present. Hammond and Welcker,<sup>21</sup> in a search for false-positive reactions for porphobilinogen in urine, studied 1,000 specimens in a random selection of patients on different services in a hospital and found no positive porphobilinogen tests. Watson,<sup>22</sup> however, in screening thousands of cases over a period of 15 years, discovered in the urines of 11 patients porphyrins other than coproporphyrin. These cases could not be classified as representing porphyria. They fall into three categories: (1) neoplastic disease, (2) severe liver disease, and (3) infectious or nervous system disease. In this latter group, Watson lists one case of Guillain-Barré syndrome. The writer believes that the patient under consideration fits into this category. To his knowledge, it is the second to be reported in the literature as a case of Guillain-Barré syndrome associated with porphobilinogenuria, uroporphyrinuria and coproporphyrinuria. One might speculate as to whether this case or the others described by Watson are latent forms of porphyria.

#### SUMMARY

A case of Guillain-Barré syndrome is presented in a patient who demonstrated the urinary excretion of porphobilinogen, uroporphyrin and coproporphyrin. Evidence in favor of a diagnosis of Guillain-Barré syndrome rather than primary porphyria is discussed. A distinction is made between "secondary porphyria," which applies to increased excretion of coproporphyrin, and the porphyrinuria observed in this patient. In addition to the increased urinary excretion of coproporphyrin, there were also demonstrated in this patient porphobilinogen and uroporphyrin.

#### ACKNOWLEDGMENT

I am indebted to Dr. Reginald Blaber, whose patient was reported in this manuscript, and who judiciously supervised the medical care.

#### SUMMARIO IN INTERLINGUA

Un puera de racia blanc de 14 annos de etate esseva hospitalisate a causa de debilitate in le gambas. Durante su soggiorno al hospital, le debilitate deveniva plus pronunciate, afficiente progressivamente le bracios, le musculos facial, e—finalmente—le musculos respiratori de maniera que le uso de un respirator esseva requirite. Omne le modalitates esseva marcatamente vitiata. A causa del sever papilledema e

del anormalmente elevate pression del liquido cerebrospinal, multiple puncturationes lumbar esseva effectuate con le objectivo de obtener decompression. Determinationes de proteina in le liquido spinal monstrava inter 200 e 600 mg pro cento ml, e inter zero e quatro leucocytos esseva trovate in omne mm<sup>3</sup>. Le examine del urina a multe occasiones revelava porphobilinogeno, coproporphyrina, a uroporphyrina. Le patiente se meliorava gradualmente. Post quatro menses de hospitalisation illa esseva dimittite e inviate a un hospital de rehabilitation.

Es discute le rationes que argue in favor de un diagnose de syndrome de Guillain-Barré plus tosto que de porphyria primari. Istos include:

1. Dissociation albuminocytologic in le liquido spinal.
2. Papilledema e elevation del pression del liquido spinal.
3. Paralyse ascendente, paresis del nervos facial, e marcate disturbance sensoria.
4. Absentia de antecedentes personal o familial de typos supportante le diagnose de porphyria.

Ben que le assertion pare justificata que le presentia de porphyrinas in le urina de iste patiente esseva probabilemente relationate a acute polyneuritis infectiose, il non se tractava hic de "porphyria secundari." Iste termino significa acceptatemente que le patiente monstra in le urina un quantitate plus que normal de coproporphyrina, un condition incontrate in un varietate de morbos. Etiam augmentos del excretion de uroporphyrina ha essite incontrate in association con le ingestion de substantias chimic e invenenamento a plumbo. In le presente patiente, porphobilinogenuria esseva constatate, e isto—il es ver—indica usualmente le presentia del morbo porphyria. Tamen, il existe in le literatura 11 reportos de casos in que porphobilinogenuria esseva demonstrate sin que le patiente manifestava ulle del symptomatas de porphyria de maniera que le diagnose de iste morbo non poteva esser proponite. Inter le mentionate 11 casos, un esseva identificate como un caso de syndrome de Guillain-Barré. In tanto que le autor lo sape, le caso hic reportate es solmente le secunde de syndrome de Guillain-Barré in association con porphobilinogenuria.

#### BIBLIOGRAPHY

1. Lyons, H. A.: Acute porphyria with spinal fluid changes, *Ann. Int. Med.* **33**: 711-717 (Sept.) 1950.
2. Yeager, C. L.: Polyneuritis; differentiation of infectious polyneuritis (Guillain-Barré syndrome) and neuritis of porphyria, *Minnesota Med.* **30**: 166-173 (Feb.) 1947.
3. Markovitz, M.: Acute intermittent porphyria: report of five cases and review of the literature, *Ann. Int. Med.* **41**: 1170-1188 (Dec.) 1954.
4. Hierons, R.: Changes in the nervous system in acute porphyria, *Brain*, **80**: 176-192 (June) 1957.
5. Freedman, A., Yeagley, J. D., and Brooks, J. B.: Acute porphyria with improvement during and following pregnancy, *Ann. Int. Med.* **36**: 1111-1120 (Apr.) 1952.
6. Hare, L., and Wilmore, R.: Acute porphyria; 2 cases with autopsy reports, *Am. J. Med.* **5**: 53-58 (July) 1948.
7. Petrie, E.: Case of acute porphyria, *Brit. M. J.* **1**: 926-929 (May 15) 1948.
8. Nesbitt, E.: Acute porphyria, *J. A. M. A.* **124**: 286-294 (Jan. 29) 1944.
9. Fisher, J. W.: Acute porphyria, *Illinois M. J.* **111**: 313-315 (June) 1957.
10. Avery, L. W.: Porphyria in relation to nervous and mental diseases, *Dis. Nerv. System* **6**: 217-221 (July) 1945.
11. Joynt, R. J.: Mechanism of production of papilledema in the Guillain-Barré syndrome, *Neurology* **8**: 8-12 (Jan.) 1958.
12. Drew, A. L., and Magee, K. R.: Papilledema in Guillain-Barré syndrome, *Arch. Neurol. and Psychiat.* **66**: 744-751 (Dec.) 1951.
13. Barnes, H. D., and Boshoff, P. H.: Ocular lesions in patients with porphyria, *Arch. Ophth.* **48**: 567-580 (Nov.) 1952.

14. Goldstein, N. P., Martin, W. J., Brunsting, L. A., and Kirby, T. J.: Blindness of cerebral origin in porphyria: report of case, *Proc. Staff Meet., Mayo Clin.* **32**: 82-87 (Feb. 20) 1957.
15. Martin, W. J., and Heck, F. J.: The porphyrins and porphyria; a review of 81 cases, *Am. J. Med.* **20**: 239-250 (Feb.) 1956.
16. Biémond, A.: Quelques remarques sur l'étiologie de la maladie de Guillain-Barré, *J. belge de neurol. et de psychiat.* **38**: 708, 1944.
17. Aring, C. D.: Infectious polyneuritis, *Clinics* **4**: 263-274 (Aug.) 1945.
18. Bassoe, P.: Guillain-Barré syndrome and related conditions (meningoradiculomyelitis and meningomyelo-encephalitis), *Arch. Path.* **26**: 289-296 (July) 1938.
19. Waldenström, J.: The porphyrias as inborn errors of metabolism, *Am. J. Med.* **22**: 758-773 (May) 1957.
20. Peters, G. A.: Acute porphyria: report of two cases with electrical studies in one, *Ann. Int. Med.* **30**: 1237-1248 (June) 1949.
21. Hammond, R. L., and Welcker, M. L.: Porphobilinogen tests on 1,000 miscellaneous patients in a search for false positive reactions, *J. Lab. and Clin. Med.* **33**: 1254-1257 (Oct.) 1948.
22. Watson, C. J.: Some studies of nature and clinical significance of porphobilinogen, *Arch. Int. Med.* **93**: 643-657 (May) 1954.
23. Watson, C. J.: Porphyria, *Advances Int. Med.* **6**: 235-299, 1954.
24. Haymaker, W., and Kernohan, J. W.: Landry-Guillain-Barré syndrome; clinicopathological report of 50 fatal cases and critique of literature, *Medicine* **28**: 59-141 (Feb.) 1949.
25. Feldman, S., Landau, J., and Halpern, L.: Papilledema in Guillain-Barré syndrome, *Arch. Neurol. and Psychiat.* **73**: 678-684 (June) 1955.
26. Gardner, W. J., Spittler, D. K., and Whitten, C.: Increased intracranial pressure caused by increased protein content in cerebrospinal fluid; explanation of papilledema in certain cases of small intracranial and intraspinal tumors and in Guillain-Barré syndrome, *New England J. Med.* **250**: 932-936 (June 3) 1954.
27. Denny-Brown, D., and Sciarra, D.: Changes in nervous system in acute porphyria, *Brain* **68**: 1-16 (Mar.) 1945.

### HEMORRHAGIC VARICELLA PNEUMONIA\*

BY JOHN G. ESSWEIN, Commander (MC) USN, and VICTOR P. DiDOMENICO, M.D., *Portsmouth, New Hampshire*

It is not generally appreciated that chickenpox, usually a benign disease in adults, may run a very severe course, or may be fatal. In recent years, papers have been published in radiologic journals describing the appearance of varicella pneumonitis in severe cases of chickenpox in adults.<sup>1,2</sup> Other papers and communications have indicated that adrenal steroid therapy may be deleterious in varicella pneumonitis.<sup>3,4</sup> The following case is presented to (1) document

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From the Department of Medicine, U. S. Naval Hospital, Portsmouth, New Hampshire. The opinions or assertions herein are the private ones of the authors and are not to be construed as reflecting the views of the Navy Department or the naval service at large.

Requests for reprints should be addressed to Victor P. DiDomenico, M.D., Director of Medical Education, Worcester City Hospital, Worcester 3, Massachusetts.

further the small number of cases of hemorrhagic pneumonitis due to varicella; (2) report the apparent improvement with cortisone therapy, and (3) emphasize the radiologic appearance of varicella pneumonitis.

#### CASE REPORT

A 37 year old white male was admitted to the U. S. Naval Hospital, Portsmouth, New Hampshire, on February 12, 1957, with chills, fever, malaise, rash and hemoptysis.

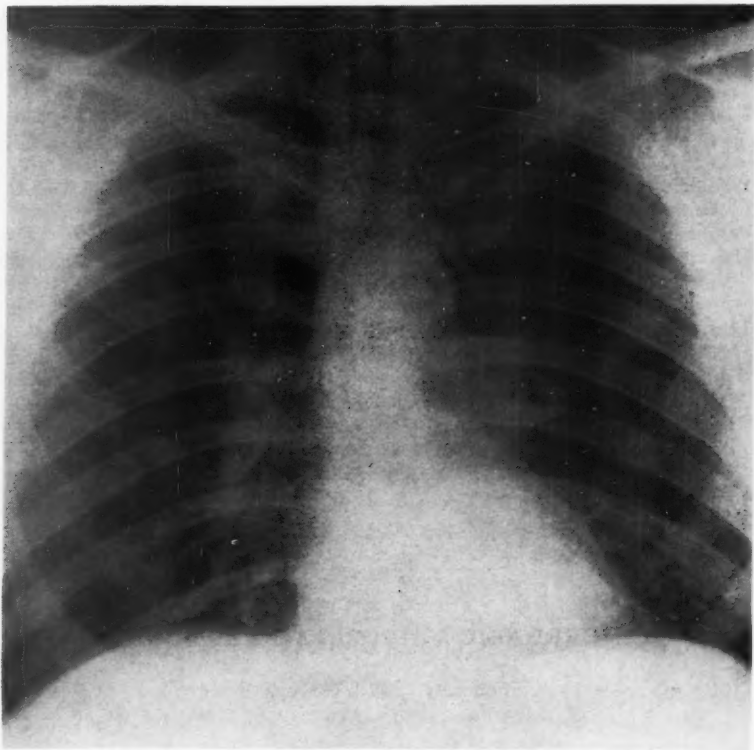


FIG. 1. Chest x-ray, February 10, 1957.

On February 3, 1957, nine days prior to admission, the patient had developed chills, feverishness and malaise. The following day he noted generalized abdominal pain, not relieved by two small bowel movements of light brown feces. He continued to have chills for the following week, with a rise of temperature to 101° F. on February 8, 1957. He was admitted to a station hospital on February 10, 1957, with a temperature of 102° F. A chest x-ray taken at this time was within normal limits (figure 1). On the morning of February 12, 1957, the patient noted small "pimples with a yellow spot in the middle" on his face and scalp. These rapidly spread to the rest of his body. Physicians described the rash as initially vesicular, rapidly becoming pustular and hemorrhagic. Through this period the patient continued to have

chills, fever and diffuse abdominal pain. On the evening of February 12, he was transferred to the Portsmouth Naval Hospital. He was still having chills and fever and, in addition, had begun to cough severely, raising large clumps of sputum which consisted chiefly of blood mixed with a small amount of mucus.

Examination at this time revealed a somewhat obese male in moderate respiratory distress who was producing large quantities of bloody sputum, and who complained of generalized abdominal aching pain and severe sharp substernal pain on coughing.

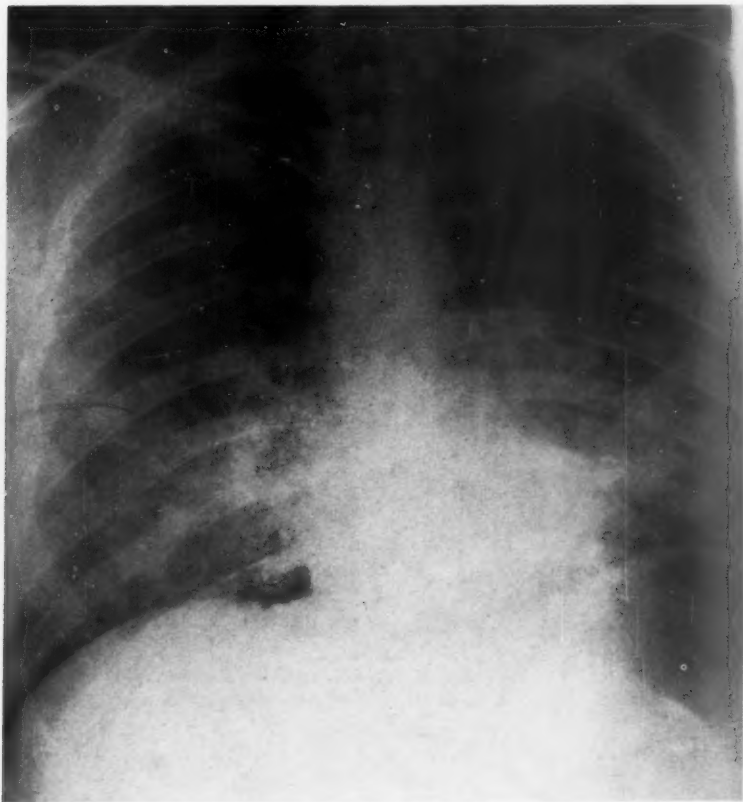


FIG. 2. Chest x-ray, February 12, 1957, showing diffuse, soft, coarsely nodular infiltrates in the lower lung fields.

Temperature, 104° F.; blood pressure, 140/70 mm. of Hg; respiration, 40; pulse, 120. A discrete vesicular rash covered all parts of the body, including the face, scalp, mouth and genitalia. These vesicles appeared to be in varying stages of development, and some appeared to be pustular and hemorrhagic. The heart sounds were rapid and regular, and without murmurs or friction rub. Auscultation revealed many wet and coarse inspiratory râles, heard over the entire chest. There was moderate tenderness in the right upper quadrant of the abdomen, and the liver edge could be palpated two fingerbreadths below the right costal margin. The spleen was not palpated.

There were palpable nodes in the axillary, inguinal and cervical regions. Rectal examination revealed dark brown feces. The prostate was normal.

Chest x-rays taken at this time showed diffuse, soft, coarsely nodular infiltrates throughout both lung fields, most prominent in the lower lung fields. Cardiac size appeared to be normal (figure 2).

By the following morning the patient appeared to be in critical condition. Overnight he had filled two and one-half cardboard sputum cups (about 500 c.c.) with

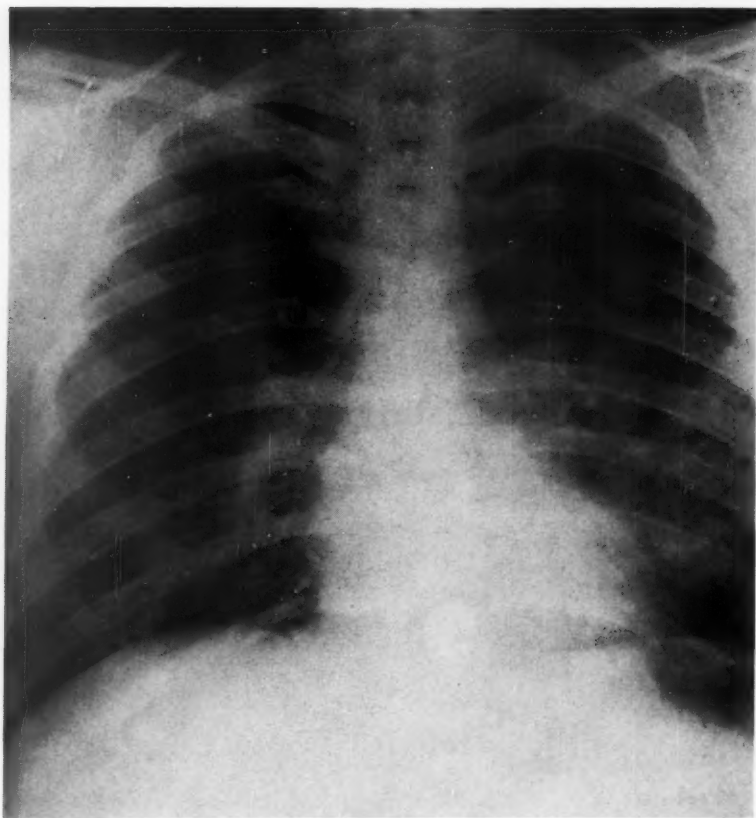


FIG. 3. Chest x-ray, March 4, 1957, showing clearing of the infiltrates.

bloody sputum. He was severely dyspneic and cyanotic, and coughed so frequently that he felt that he was "choking to death on [his] own blood." At this time his temperature was 101.4° F.; pulse, 110; respiration, 40. He was put into an oxygen tent and started on cortisone, 100 mg. three times a day, and tetracycline, 250 mg. every four hours.

About 12 hours following the institution of the above therapy the patient had improved markedly. Temperature, 99.2° F.; pulse, 88; respiration, 20. His cough persisted but was less painful, his sputum less bloody.



On February 14, 1957, the third hospital day, the patient continued to improve symptomatically, and it was noted that the last crop of vesicles appeared on the palms of his hands. Wet and coarse râles persisted in his chest. His cough was somewhat improved, and the sputum had become mucopurulent, with bright and dark red clumps of blood.

By the following day the temperature had dropped to normal; pulse was 80 and respiration 20. The patient was no longer dyspneic out of oxygen. His cough was less productive, and sputum was now only blood-streaked.

On the sixth hospital day he was taken out of oxygen, and only coarse râles were heard in his chest. He was afebrile; pulse was 62, respiration, 20.

The following morning the patient passed a very large, greenish black stool, which was guaiac-positive. He had been on a liquid diet. His sputum no longer contained blood and was markedly diminished in amount.

Gradually, over the course of the next week, the patient's cough improved, he became asymptomatic, and his skin lesions crusted and largely healed. Follow-up chest x-rays taken on February 19, February 26 and March 4, 1957 (figure 3), showed progressive clearing of the chest. Laboratory studies were as follows: white blood cell count, 12,900 on admission, 22,200 three days following admission; hemoglobin, 13.9 gm.%; hematocrit, 45; thymol turbidity, 6.4; cephalin flocculation, 2 plus in 48 hours; serum bilirubin, 0.8 mg.%; prothrombin time, 100% of normal; Lee-White clotting time, 6 minutes; Rumpel-Leede, normal; bleeding time, 3 minutes, 45 seconds. Urinalysis: specific gravity, 1.025; albumin, 0; sugar, 0; sediment, normal. Nonprotein nitrogen, 38 mg.%; fasting blood sugar, 93 mg.%. The Kahn test was negative. An electrocardiogram was within normal limits. Sputum culture grew out alpha streptococcus and *Staphylococcus aureus*. A gastrointestinal series and Graham Cole tests were within normal limits.

#### DISCUSSION

Review of the literature indicates that the first implication of the varicella virus in the etiology of pneumonitis was by Waring et al. in 1942.<sup>5</sup> In 1956 Southard<sup>6</sup> reviewed the severe cases of varicella pneumonia and presented a synthetic "typical severe adult case." The case herein presented appears to be more severe than her "typical case" because of marked cyanosis and hemoptysis. In addition, there was probably gastrointestinal bleeding, as evidenced by the severe abdominal pain, tenderness and black stools which were guaiac-positive. However, it is possible that the patient swallowed some of the hemorrhagic sputum.

Few of the cases reported have shown marked hemoptysis. In the severe viral group of 19 cases reported by Weinstein and Meade,<sup>7</sup> only three had sputum containing bright red blood, and marked hemoptysis (more than a cupful) was not found in these cases. In this group it was also noted that the "skin eruption" was extensive and severe in all cases, and hemorrhagic in four; death occurred in two of the latter.

The nature of the hemorrhagic diathesis in varicella is obscure. In one case reported by Cohen and Bansmer,<sup>8</sup> definite idiopathic thrombocytopenic purpura was observed, proved by marrow biopsy and repeated platelet counts. In only one of the cases reported by Weinstein and Meade<sup>7</sup> was thrombocytopenia noted, and in those who had hemorrhagic skin eruptions, abnormal coagulation of blood or platelet deficiency was not found.

Study of the pathologic material by Waring et al.<sup>5</sup> in a fatal case of chickenpox showed:

1. Chickenpox vesicles, severe, generalized.
2. Encephalitis, acute, toxic, moderately diffuse, with purpuric lesions in the white matter.
3. Lobar pneumonia, severe, confluent, mononuclear, proliferative.
4. Nephrosis, acute, toxic, moderate.

It has been stated that corticosteroids should not be used in chickenpox because of the possibility of reactivating the infection and producing a more severe disease. This is probably true for the average case. However, the mechanism of severe complications in chickenpox—namely, viral pneumonitis, hemorrhage, nephrosis, encephalitis and idiopathic thrombocytopenic purpura—is not at all clear, and may well represent, in those individuals, who develop severe complications other than bacterial, a hyperimmune reaction to either the virus of chickenpox or to products elaborated by it.

Treatment with cortisone in the present case was followed by prompt remission; however, it is not known whether this was coincidental or whether the corticosteroid played a role in the rapid improvement.

Because the patient appeared to be in extremis, it was felt that the use of corticosteroids was indicated. As may be noted in the case report, the signs and symptoms cleared rapidly within the course of 12 hours after the initiation of this therapy. This would appear to us to be in contrast to the course in the five cases reported by Southard,<sup>6</sup> which showed clearing of symptoms by lysis despite all therapy. It is suggested that the hemorrhagic lesions in the lungs, skin and gastrointestinal tract may well represent generalized vasculitis, or an immunovascular phenomenon secondary to varicella infection.

Comparison of figures 1, 2 and 3 with illustrations presented by Tan et al.<sup>9</sup> shows the typical appearance described by these authors. This consists of a nodular infiltration involving mainly the lower two thirds of the lung fields.

#### SUMMARY

A case is presented of hemorrhagic varicella pneumonia treated with cortisone. Rapid recovery appeared to follow institution of this therapy. However, the improvement noted may have been entirely coincidental. There was no reactivation of the disease process in this case.

#### SUMMARY IN INTERLINGUA

Varicella es usualmente un morbo benigne. Tamen, in adultos manifestationes sever es a vices incontrate.

Es presentate le caso de un masculo de 37 annos de etate qui esseva hospitalisate con le lesiones cutanee typic de varicella. Brevemente post su admission, ille developpava hemoptysis profuse, cyanose, e grossier e humide rhonchos in omne partes del thorace. Su temperatura montava a 104 F, e le roentgenogramma revelava pneumonia nodular que esseva le plus prominente in le campos inferior del pulmon.

Proque le patiente esseva apparentemente al puncto del morte, ille esseva tractate con oxigeno, cortisona (100 mg, tres vices per die), e tetracyclina (250 mg, omne

quatro horas). Al fin de 12 horas, le melioration esseva marcate. Le restablimento se compleva sin complicationes additional.

Es suggerite le possibilitate que un vasculitis generalisate es le causa del manifestationes hemorrhagic in le casos sever de infection per varicella. Il non es possibile asserer que le corticosteroides esseva de adjuta in le restablimento de iste patiente. Es sublineate de novo le apparentia roentgenologic de pneumonia a varicella, que consiste de un infiltration nodular in le duo tertios inferior del campos pulmonar.

#### BIBLIOGRAPHY

1. Kriss, N.: Chickenpox pneumonia, a case report, *Radiology* **66**: 727-729, 1956.
2. Endress, Z. F., and Schnell, F. R.: Varicella pneumonitis, *Radiology* **66**: 723-726, 1956.
3. Shee, J. C., and Fehrsen, P.: Reactivation of varicella virus by cortisone therapy, *Brit. M. J.* **2**: 82, 1953.
4. Haggerty, R. J., and Eley, R. C.: Varicella and cortisone, *Pediatrics* **18**: 160-162, 1956.
5. Waring, J. J., Neuburger, K., and Geever, E. F.: Severe forms of chickenpox in adults, *Arch. Int. Med.* **69**: 384-408, 1942.
6. Southard, M. E.: Roentgen findings in chickenpox pneumonia, *Am. J. Roentgenol., Rad. Therap. and Nucl. Med.* **76**: 533-539, 1956.
7. Weinstein, L., and Meade, R. H.: Respiratory manifestations of chickenpox, *Arch. Int. Med.* **98**: 91-99, 1956.
8. Cohen, J. J., and Bansmer, C.: Chickenpox with simultaneous idiopathic thrombocytopenic purpura, *New England J. Med.* **237**: 222-224, 1947.
9. Tan, D. Y. M., Kaufman, S. A., and Levene, G.: Primary chickenpox pneumonia, *Am. J. Roentgenol., Rad. Therap. and Nucl. Med.* **76**: 527-532, 1956.

## EDITORIALS

### *IN PARTING*

THE Editor of the *ANNALS OF INTERNAL MEDICINE*, after holding this position for 27 years, has come finally this month to the last issue which will show his name at the masthead.

It is natural at such a time to look back over the years—back to the youth of the journal, when it was sometimes difficult to select from the scant offerings sufficient manuscripts to fill a thin issue—back to the years when the College was small and its members comprised nearly the whole list of subscribers. One reviews in one's mind the steady expansion that has occurred in the number of both contributors and subscribers. At present, many valuable manuscripts must be turned away for lack of space, though the size of each issue has more than doubled. The membership of the College during this same period has quadrupled, but today these members constitute only one-half of the total subscribers to the *ANNALS*.

This steady growth of the *ANNALS* is due primarily to those authors who have selected this journal as the medium through which to present their clinical observations and the results of their investigations to the medical world. To the several thousand contributors who, by submitting their work for publication in the *ANNALS*, have ensured the success of this journal, a debt of gratitude is acknowledged.

The Editor has always received encouragement and assistance from the Committees and Boards which from time to time have succeeded each other in the task of representing the Regents' interest in the College journal. The administrative office in Philadelphia, until recently under Mr. Edward R. Loveland, has coöperated in the friendliest spirit whenever the business affairs of the *ANNALS* and the activities of the Editor's office overlapped. No small debt of gratitude is also owed to the officers and to the staff of the Lancaster Press.

The Editor's office surveys manuscripts submitted, edits and sees through the press those that are accepted. In the accomplishment of these tasks the Editor is only the leader of a team each member of which has an indispensable part to play. The Associate Editor, Dr. Paul W. Clough, the Assistant Editors, past and present, the Editorial Assistants, the consultant readers have all worked with the Editor with such devotion to the common task that these years of association and joint effort will always be a happy memory.

The Editor's own task has been a rewarding one. Not only has it afforded him an unexampled opportunity to view the panorama of medical progress, but it has also made it possible for him to keep in close contact with the affairs of the College, an institution which he has always been glad to serve.

Such shadows as attend the separation from an absorbing avocation are lightened for the Editor by the assurance he feels that his successor, Dr. J. Russell Elkinton, has not only the same conception of the objectives of this journal, but also, through his wide experience in clinical science and teaching, has demonstrated the capacity to maintain and to advance further the standards of the *ANNALS OF INTERNAL MEDICINE*.

MAURICE C. PINCOFFS

### *MAGNESIUM DEFICIENCY*

MAGNESIUM deficiency arising spontaneously in cattle has been well known for three decades.<sup>1</sup> It has repeatedly been produced experimentally and studied extensively in animals, particularly in rats.<sup>2</sup> In man, however, it has been infrequently recognized, and until recently its manifestations as distinguished from those of other associated deficiencies had not been clearly established.

Magnesium is widely distributed in food, in both plants and animals, and almost any human diet amply supplies the need under ordinary circumstances. A greatly increased requirement, however, or progressive depletion in conjunction with an inadequate intake may cause outspoken symptoms of deficiency.

In cattle, manifestations are ordinarily limited to the first two weeks after being turned out to pasture in the spring, particularly in heavily fertilized fields. This has been attributed to a high content of nitrogen in the grass at that season. It has been shown that increasing the protein in the diet (or also the potassium or calcium) increases the need for magnesium and may precipitate symptoms in subjects with a borderline deficiency. The grass contains adequate magnesium, but it has been claimed that the latter is inadequately absorbed from the gastric rumen, the contents of which are strongly alkaline under these circumstances. Feeding additional magnesium, however, will usually avert this trouble. The syndrome less often appears also in calves which have been kept for an unduly long period on an exclusively milk diet, "lactation tetany."

Magnesium is widely distributed in the body, the total quantity, a little over 20 grams in an average subject, being exceeded only by that of the electrolytes, sodium, potassium and calcium. A little over half of the magnesium is in bone, and of the balance, according to Shohl,<sup>3</sup> about 9.5 gm.

<sup>1</sup> Sjollem, B.: Nutritional and metabolic disorders in cattle, *Nutrition Abstr. and Rev.* 1: 621-632, 1932.

<sup>2</sup> Kruse, H. D., Orent, E. R., and McCollum, E. V.: Studies on magnesium deficiency in animals. I. Symptomatology resulting from magnesium deprivation, *J. Biol. Chem.* 96: 519-539, 1932.

<sup>3</sup> Shohl, A. T.: *Mineral metabolism*, 1939, Reinhold Publishing Co., New York, pp. 19, 20.

are within the cells and 0.5 gm. in the extracellular fluids, including the blood plasma. Next to potassium, magnesium is the most abundant intracellular electrolyte, and it is essential for the activity of many intracellular enzymes of vital importance.

For practical purposes the small fraction of the magnesium present in plasma is the only portion accessible for clinical investigation. The normal concentration is relatively low, about 1.8 to 2.2 mEq. per liter. Methods for determining magnesium have been relatively difficult and tedious and until recently lacked precision, although current spectrophotometric methods are reported to be more satisfactory. There is, however, no close correlation between the concentration of magnesium in the serum and the severity of clinical symptoms, and deviations of both types occur—a low serum level with no symptoms and a normal or even high level with depletion as indicated by clinical symptoms and by a positive balance (retention of magnesium) in metabolic studies while magnesium is being administered.

The intracellular magnesium appears to be avidly retained, relatively little being lost in depleted animals. In young animals considerable magnesium (from 30% to 40%) may be abstracted from bone to meet other needs, but the possibility of the utilization of such magnesium by adult human subjects has been questioned. These discrepancies together with the intermingling of symptoms of other deficiencies have rendered recognition of human cases of depletion more difficult.

The characteristic symptoms were first identified in cattle with "grass staggers." Such animals become restless, "nervous," and show muscular tremor and twitching which have been termed tetany. Their behavior becomes peculiar, they lose appetite, leave the herd, look dazed, confused or become wildly excited, they may low continuously, become ataxic and unsteady and in the preterminal stage have generalized convulsions, the first of which may be fatal. The concentration of magnesium in the blood is usually reduced. In the earlier stages magnesium by mouth will arrest the disturbance, but parenteral injections may be required if the symptoms are severe.

The experimental disease in young rats on a diet deficient in magnesium closely resembles the above description.<sup>2</sup> There is a preliminary period of intense cutaneous vasodilatation, followed by irritability, hyperexcitability, muscular twitchings and eventually fatal convulsions. In less acute forms there is an arrest of growth, malnutrition and cachexia, with renal injury characterized by tubular degeneration and atrophy and fibrosis of the corticomedullary regions. There are extensive lesions in the cerebellum, with degeneration of the cortical cells, particularly of the Purkinje cells, as well as hepatic and myocardial degenerative changes.

Tetany and associated symptoms in man attributable to a deficiency of magnesium were recognized many years ago. The diagnosis was based usually on the demonstration of a low level of magnesium in the blood and



by exclusion of a hypocalcemia and an alkalosis. In the early reports, however, the participation of associated deficiencies in the development of these symptoms was not adequately excluded.

In an early study, Hirschfelder<sup>4</sup> reported 13 cases of severe renal disease with high blood magnesium, associated with varying degrees of drowsiness or even coma, as might be anticipated from its well known pharmacologic effect as an anticonvulsant and in high concentrations of 8 to 10 mEq. per liter, as an anesthetic. Hirschfelder also reported 10 cases with low magnesium levels, exhibiting muscular twitchings or even convulsions. Four of these were patients with uremia whose twitchings and in one case convulsions were checked by the administration of magnesium sulfate. In subsequent years occasional similar cases of magnesium deficiency were reported, chiefly in patients with severe renal disease or toxemia of pregnancy, but also occasionally in other depleted states such as malignant disease, and in hyperthyroidism and hyperparathyroidism.<sup>5</sup> Symptoms of deficiency may be precipitated by copious diuresis such as may follow the use of ammonium chloride and mercurial diuretics in cardiac disease with congestive failure or cirrhosis of the liver with ascites, or the successful control of severe diabetic acidosis.<sup>6</sup>

The variable findings in severe renal disease may depend upon the precise way in which function is disturbed. In a healthy subject with normal stores, magnesium administered parenterally is excreted in the urine almost quantitatively. It passes freely into the glomerular filtrate, but it may be reabsorbed in varying degree in the tubules. If the stores of magnesium are depleted it may be largely reabsorbed, even with a normal blood level. If the tubules are sufficiently damaged, however, absorption will be reduced and wastage of magnesium may occur even though the stores are depleted. If the damage is such as greatly to reduce the glomerular filtrate, magnesium will accumulate and doubtless may contribute to the uremic syndrome.

During the past decade more adequate studies have been made and the manifestations of magnesium deficiency more clearly defined, although the earlier clinical descriptions have been largely confirmed.<sup>7,8</sup> Initial symptoms are often nervousness and agitation, ataxia, tremor and muscular twitching which may progress to choreiform or more rarely athetoid movements. There may be facial or carpopedal spasm with positive Chvostek and Trousseau signs, like the tetany of hypocalcemia, which indeed may coexist. It is distinguishable by a normal blood calcium level and by the

<sup>4</sup> Hirschfelder, A. D., and Haury, V. G.: Clinical manifestations of high and low plasma magnesium, *J. A. M. A.* **102**: 1138-1141, 1934.

<sup>5</sup> Ravdin, J. S., and Johnston, C. G.: Clinical significance of magnesium deficiency and its relation to parathyroid disease, *Am. J. M. Sc.* **235**: 206-219, 1958.

<sup>6</sup> Martin, H. E., Mehl, J., and Wertman, M.: Clinical studies of magnesium metabolism, *M. Clin. North America* **36**: 1157-1171, 1952.

<sup>7</sup> Randall, R. E., Jr., Rossmeisl, E. C., and Bleifer, K. H.: Magnesium depletion in man, *Arch. Int. Med.* **50**: 257-287, 1959.

<sup>8</sup> Wacker, W. E. C., and Vallee, B. L.: Magnesium metabolism, *New England J. Med.* **239**: 431-438, 1958 (a review).

fact that calcium given intravenously does not check the disturbance and may aggravate it. With this, mental disturbances are usual—delirium, confusion, hallucinations, sometimes with great excitement and violent behavior, followed later by stupor and coma in the severest cases, particularly in cirrhotics, with generalized convulsions which may be fatal if neglected. There may be a state of hyperexcitability in which convulsions can be precipitated by trivial external stimuli such as a loud hissing sound.

These disturbances can usually be controlled by the timely administration of magnesium sulfate parenterally, usually given intramuscularly in 50% solution, 1 to 2 grams four times a day for several days. The effect is not immediate, however, even if given intravenously. There is usually an interval of at least several hours and sometimes two to four days before the disturbances are substantially relieved. This supports the view that the significant trouble is intracellular, probably a need for more intracellular magnesium even though no definite deficiency within the cells has been demonstrated. It has also been suggested that a disturbance of the ratio of the intracellular to extracellular concentration of magnesium is at fault. Even after magnesium is immediately available, some little time is evidently required to make the necessary readjustments.

Magnesium exerts both a central and a peripheral action on the nervous system.<sup>8</sup> A deficiency tends to cause an excitability and irritability; an excess produces the well known sedative and anticonvulsant action. Peripherally a lack of magnesium lowers the threshold of stimulation of the motor nerves, increases the liberation of acetylcholine and facilitates transmission of the impulse at the motor end plate and increases the contractility of the muscle. An excess exerts the opposite effect, blocking transmission at the neuromuscular junction like curare which acts as an adjuvant. Although the net effect of a calcium deficiency is to increase transmission of the impulse, its action on the end plate is antagonistic to that of magnesium and of curare.

A large number of cases of magnesium deficiency has been reported by Flink et al.,<sup>9, 10, 11</sup> who have especially pointed out the frequency of such deficiency in severe chronic alcoholism. They reported studies of 29 cases of chronic alcoholism with delirium tremens and of 21 cases with tremor and twitching but no delirium.

They also observed 10 additional cases with similar clinical symptoms in non-alcoholics. In all severe cases there was both a diminished intake and an increased loss of magnesium. The loss might be the result of diarrhea, vomiting, gastric suction, or profuse diuresis, accompanied usually by the

<sup>9</sup> Flink, E. B., Stutzman, F. L., Anderson, A. R., Konig, T., and Fraser, R.: Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens, *J. Lab. and Clin. Med.* **43**: 169-183, 1954.

<sup>10</sup> Flink, E. B.: Magnesium deficiency syndrome in man, *J. A. M. A.* **160**: 1406-1409, 1956.

<sup>11</sup> Flink, E. B., McCollister, R., Prasad, A. S., Melby, J. C., and Doe, R. P.: Evidences for clinical magnesium deficiency, *Ann. Int. Med.* **47**: 956-968, 1957.

parenteral administration of large volumes of fluid containing sodium, potassium, often calcium, and glucose or other nutrients, but without magnesium. These included patients with complicated chronic peptic ulcer, cholecystitis, and various untoward complications and accidents following major surgical operations. Treatment with magnesium sulfate usually relieved the alarming neurologic and psychiatric disturbances, and in several who relapsed when treatment was stopped prematurely, a second course again gave relief.

The resemblance of the symptoms of these patients to those observed in the cases of delirium tremens suggested that the latter might also be suffering from magnesium depletion. This was found in general to be the case, and when these patients were grouped in three classes according to the apparent severity, there was a correlation with the mean concentrations of serum magnesium in each group, although there were individual exceptions. Flink et al. treated 44 patients, 26 with magnesium and 16 by conventional measures only. In the treated group there was a reduction of the average duration of the major symptoms which was statistically significant with respect to some of these symptoms.

Suter et al.<sup>12</sup> studied the levels of magnesium in the serum of a large series of neurologic and psychiatric patients and found it reduced only in the severe chronic alcoholic group, confirming Flink "entirely." These patients were benefited by treatment with magnesium. A small proportion of their epileptic patients were also found to have a low serum magnesium, but these were not so benefited.

Randall et al.<sup>7</sup> have also reported a study of 12 cases, all malnourished subjects, chiefly with chronic alcoholism, with a history of profuse vomiting in seven and diarrhea in seven. Parenteral administration of fluids had been carried out in 11. The onset of symptoms was abrupt, with a psychosis in seven and with mild confusion in four others, beginning a few days before the appearance of the muscular twitchings (in 11), fasciculations, rhythmic tremor and (in two) convulsions. The blood magnesium level was low in 10, and in the two others the retention of magnesium during treatment indicated that the body stores had been depleted. Parenteral administration of magnesium in six and restoration of an adequate diet in six others resulted in retention of magnesium with restoration of the depleted stores and in relief of symptoms. In two, however, a potassium depletion had first to be restored. In several the serum magnesium fell later, without the reappearance of symptoms, presumably because the body stores were still adequate, again indicating the unreliability of the serum level as sole indicator of the state of the magnesium metabolism.

More recently Vallee and Wacker<sup>13</sup> have reported studies on five patients with tetany due to magnesium deficiency, chiefly cases of severe alcoholism.

<sup>12</sup> Suter, C., and Klingman, W. O.: Neurologic manifestations of magnesium depletion states, *Neurology* 5: 691-699, 1955.

<sup>13</sup> Vallee, B. L., and Wacker, W. E.: The magnesium deficiency tetany syndrome in man, *New England J. Med.* 262: 155-161, 1960.

They stress the clinical similarity to hypocalcemic tetany which they could distinguish only by chemical tests. They confirm the low magnesium in these alcoholics but question whether the low magnesium level is the sole or the major cause of the delirium. In one of these patients, who had severe tetany and convulsions but was lucid in the intervals, treatment with magnesium sulfate relieved tetany and restored a normal blood level quickly. A few days later, however, with the serum magnesium still normal, delirium tremens first appeared, clearing up shortly with sedation and the usual conventional measures.

It is obvious that these severely ill alcoholics must suffer multiple deficiencies, and it is futile to expect simple restoration of magnesium alone to restore them entirely to normal. It is equally obvious that a majority of these patients with delirium tremens eventually recover without the administration of magnesium other than that included in an adequate diet. Possibly enough magnesium may still be obtainable from bone to tide them over the acute emergency.

This brief review indicates clearly that under special circumstances a serious depletion of magnesium can occur and that it gives rise to a fairly characteristic syndrome, even though not pathognomonic to the point that it can be differentiated with certainty from other deficiencies by clinical means alone. The picture may be further confused by manifestations of hepatic dysfunction. It seems highly probable, however, that the muscular hyperexcitability and "tetany" in delirium tremens are due in substantial part to a depletion of magnesium and that this also contributes to the production of the psychiatric disturbances.

If the possibility of such a depletion is realized, it should usually be simple to prevent it or control it. Magnesium, unlike calcium, is readily absorbed from the digestive tract without the assistance of any hormone, and oral administration would usually suffice. Other deficiencies should not be neglected, but the administration of large amounts of potassium or calcium to relieve deficiencies of these electrolytes is likely to aggravate symptoms of magnesium deficiency if the latter is neglected. In case of vomiting or in patients receiving large amounts of fluid parenterally, many such crises could probably be avoided by adding magnesium to the usual infusions or by administering it intramuscularly.

PAUL W. CLOUGH

## REVIEWS

*Radioisotope Studies of Fatty Acid Metabolism.* (Volume I of Division VI: Medicine, International Series of Monographs on Nuclear Energy; General Editors: R. A. CHARPIE and J. V. DUNWORTH). By JAMES F. MEAD and DAVID R. HOWTON, Department and Laboratories of Nuclear Medicine and Radiation Biology, University of California, Los Angeles. 141 pages; 22 × 14.5 cm. Pergamon Press, Inc., New York. 1960. Price, \$7.50.

Heightened interest in fat metabolism followed demonstrations in the early 1940's that body fats were in a state of dynamic fatty acid exchange rather than simply inert storage substances as they had been thought to be. The availability of long-lived radioactive carbon isotope,  $C^{14}$ , permitted rapid advances toward eventual delineation of the pathways of fat metabolism. During the 10 years that radioactive isotopes were applied to this problem, many aspects of fat and fatty acid metabolism were clarified; others, only approached. Frazer's radical "partition" theory of fat absorption was shown to be valid to the extent that short chain fatty acids (8 to 12 carbons) are completely absorbed into the portal blood while long-chain fatty acids are completely absorbed by the lymphatics. Functions of the phospholipids remained unclear although a role in the transport of  $\alpha$ -lipoproteins seemed established. The energy role of a primitive lipoprotein, fatty acid albumin complex, derived from hydrolysis of triglycerides of peripheral tissues, is suggested. The need for further study of fatty acid mobilization and depot fat is emphasized. Turnover studies of acetate and fatty acids are mentioned. Relationships of carbohydrate and fatty acid metabolism are discussed. Knoop's classical theory of beta oxidation of fatty acids was confirmed. The dynamic nature of fatty acid metabolism is further emphasized in a review of alteration, interconversion and carbohydrate conversion experiments. The complexity of sterol and sterol ester formation is recognized. The controversy over hepatic and intestinal roles in sterol ester formation continues. Several pages are devoted to consideration of the future applications of radioactive isotope studies of lipid metabolism. Appendices provide references which deal with the laboratory synthesis of labeled fatty acids and with the controlled degradation of labeled fatty acids.

A tremendous amount of material has been condensed into this book. The bibliography is extensive and well annotated. The authors have accomplished their avowed purpose, "... to show how tracer studies have contributed to our knowledge of fatty acid metabolism." The book should be valuable to biochemists entering the field of radioactive isotope studies of fatty acid metabolism and to busy clinicians seeking a condensed review of the important work in this field.

V. M. S.

*Individuum und Krankheit: Grundzüge einer Individualpathologie.* By Professor Dr. FRIEDRICH CURTIUS. 467 pages; 25.5 × 17.5 cm. Springer-Verlag, Berlin. 1959. Price, DM 88.-.

This book is the result of a lifelong scholarly study of a most important aspect of general medicine which often is being neglected in teaching: the role of the individual in pathogenesis. Curtius does not handle the problem from the psychological or psychiatric point of view alone; rather on the basis of the knowledge of an experienced clinician who is constantly aware of the complex and multiple causes of disease in each individual patient. Historical generalizations and unilateral aspects of successful discoveries in laboratory technic have, in the past, minimized the importance of individual factors. Constitutional and anthropological types also were

conceived as group phenomena. Curtius deals with prominent representatives of different schools of thought—contemporary and past—with proper citation, and he challenges their methods.

The purpose of his book is to give individual pathology the merits of a scientific method and elevate its application above empiric intuition. The author illustrates his ideas in numerous examples and always points out family history and genetic background as well as previous disease and other constitutional factors which modify the "morbus compositus." The typical detail of a textbook diagnosis is too limited for the endless variety of what actually is happening in the individual patient. A better analysis of these principles is important for the best choice of the therapeutic procedure in the individual patient as well as in their legal interpretation in compensation cases.

This monograph is a very personal book, but it cannot be overlooked.

RUDOLF ENGEL

*The Acute and Chronic Peptic Lesions of the Stomach and the Duodenum: Their Frequency, Mutual Relation and Correlation with Other Diseases.* By IZAK SALOMON LEVIJ. 104 pages; 24 × 16 cm. (paper-bound). Uitgeverij Excelsior, Oranjeplein 96, 'S-Gravenhage, Holland. 1959. Price: Equivalent of \$1 in countries other than Holland.

Current medical literature reflects unrelenting attempts to correlate peptic ulcer with "this or that" disease entity, or to regard peptic lesions as secondary to some pathologic condition elsewhere in the body. The purpose of this monograph has been the investigation and the analysis of a large autopsy material with a view to studying the frequency and the mutual relations of peptic lesions to other diseases. The author's analysis is based on 11,964 necropsies performed in Rotterdam from 1940 to 1956.

Part one describes the analyzed material and the methods used in the investigation. Part two attempts to correlate peptic lesions with other pathologic conditions. Included is a review of the literature for the past century on the frequency and the associations of peptic ulcer. Critical analysis of these reports reflects the artificial differences caused by various methods of investigation: for example, the bias introduced by the prejudice of an investigator when only one disease is chosen to be correlated with peptic ulcer.

The most important result of this investigation has been the demonstration of a positive correlation between peptic lesions and chronic pulmonary disease. Concerning the genesis of these lesions the concept has been evolved of initiating and chronicity-promoting factors.

This monograph should appeal to the minority of physicians who endeavor to correlate peptic ulcer with some other disease entity.

J. E. K.

*Diseases of Medical Progress: A Survey of Diseases and Syndromes Unintentionally Induced as the Result of Properly Indicated, Widely Accepted Therapeutic Procedures.* By ROBERT H. MOSER, B.S., M.D. 131 pages; 22.5 × 14 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1959. Price, \$4.75.

Modern methods of treatment have altered profoundly the natural histories of many diseases which formerly caused prolonged, severe illness or death. In the course of these developments abnormal conditions not previously encountered have come into being or been unmasked. A great variety of syndromes, varying in degree from mild to fatal, have been recognized. These states, referred to as "diseases of medical progress," are described by Dr. Moser.



The author has attempted to produce an all-inclusive compilation of abnormalities said to result from newer therapeutic technics. To this end, he has set up categories under which are listed numerous therapeutic factors purported to produce the specific aberration. The bibliography exceeds 700 items, occupying more pages than the text. The value of this book is considerable. It serves to remind one of the hazards associated with modern therapy, and the reader is supplied with guides to the early recognition of these dangers. The extensive bibliography serves a source function, enabling the physician to consult the original reports pertaining to a problem in this sphere.

There are some weaknesses in the volume. Overwriting and flowery sentence formation decrease its readability. Very little space is devoted to the physiological or biochemical bases for the syndromes encountered. Critical discussion of the material is kept to a minimum.

In a field which moves as rapidly as this one, frequent revisions of a book are necessary to keep it from becoming obsolete. The reviewer hopes that the second edition of *Diseases of Medical Progress* will be even more useful than the first.

J. E. C.

*Methods in Medical Research*. Volume 8. H. D. BRUNER, Editor-in-Chief. 368 pages; 22 × 14 cm. The Year Book Publishers, Inc., Chicago. 1960. Price, \$9.75.

This is the eighth in this well-known series of books designed to present the details of research methods currently used by active investigators. The volume contains three sections:

Life History of the Erythrocyte, Walter S. Root, Editor  
Measurement of Responses of Involuntary Muscle, A. M. Lands, Editor  
Peripheral Blood Flow Measurement, H. D. Bruner, Editor

Persons familiar with previous volumes will recognize that the section on blood flow in this volume, plus the section on Hemodynamic Methods—Heart and Lungs, in Volume 7, supplement and bring up to date the section on Circulation that appeared in Volume 1 twelve years ago. Similarly, the sections in this volume on The Erythrocyte and Smooth Muscle supplement, respectively, the sections in Volume 7 on the Leukocyte and Muscular Tissues in general.

The presentations maintain the same high degree of excellence as was true of previous volumes.

B. W. A.

*A Symposium on pH and Blood Gas Measurement: Methods and Interpretation*. Edited by RONALD F. WOOLMER, V.R.D., B.A., B.M., F.F.A.R.C.S.; assisted by JOY PARKINSON, B.A. 210 pages; 22.5 × 14 cm. Little, Brown and Company, Boston. 1959. Price, \$8.50.

In December 1958 the Ciba Foundation sponsored a two day symposium on The Measurement of Blood Gases and pH. This volume contains the papers presented as well as a record of the numerous discussions. Most of the participants are British; one, Dr. P. Astrup, is from Denmark; and Dr. John Severinghaus is from the U.S.A.

This book has most of the shortcomings that such reports usually have such as, overlapping of material presented by different persons and the ambiguity that results when verbatim records of spoken statements are written out; also, it consists of many facets of the subject rather than a comprehensive unified presentation. However, the worst feature is the title, which is misleading: The symposium actually deals with

measurement of pH and  $\text{CO}_2$  tension; measurement of  $\text{O}_2$  tension is considered only briefly; blood gas contents are not mentioned. Thus, a better title would be something like, "Measurement of the pH of Blood in Clinical and Experimental Medicine." From this standpoint, this is the best available single source of information and reference material on the subject. One very good feature is the record of discussions; these contain many frank statements of divergent opinions as well as different approaches, both theoretical and practical, to similar problems. The actual papers are uniformly excellent and each lists a group of current references.

People interested in the pH and  $\text{PCO}_2$  of blood will find that this book does an excellent job of filling the gap between the more elementary and clinical discussions of Straumfjord in *Standard Methods of Clinical Chemistry*, Volume II, Academic Press, 1958; Belcher in *Medical Physics*, Volume 1, The Year Book Publishers, Inc., 1944; or Moller in *Acta Medica Scandinavica*, Volume 165, 1959; and the more advanced treatments, such as Bates, *Electrometric pH Determinations*, John Wiley & Sons, Inc., 1954.

B. W. A.

*Atomic Medicine*. 3d Ed. Edited by CHARLES F. BEHRENS, M.D., F.A.C.R., Rear Admiral, MC, U. S. Navy (Ret.); Roentgenologist, The Yater Clinic, Washington, D. C.; Consultant and Lecturer in Radiology, U. S. Naval Medical Center, Washington, D. C. 705 pages; 16 × 23.5 cm. The Williams and Wilkins Company, Baltimore, Maryland. 1959. Price, \$15.00.

In 1949, the initial edition of this volume appeared as one of the earlier and better works devoted solely to the then new field of atomic medicine. By 1953, the author decided that sufficient changes had taken place in the field to warrant a second edition and this appeared to be greeted eagerly by physicians interested in the subject. In 1959, ten years after the initial edition of *Atomic Medicine*, the latest edition, but not necessarily the best, was published.

The third edition is some 75 pages and two chapters longer than its predecessor and eight new contributing authors have been added to the group. There is a great deal of valuable information in the book but an excessive amount of detail tends to obscure it.

It would appear to this reviewer that the author has attempted to cover in too complete a manner a multifaceted and complex field. In doing so, a cumbersome tome has been created. There are now several more readable and less expensive volumes available to those interested.

J. B. W.

*Pain and Itch: Nervous Mechanisms* (Ciba Foundation Study Group No. 1). Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and MAEVE O'CONNOR, B.A. 120 pages; 19 × 12.5 cm. Little, Brown & Company, Boston. 1959. Price, \$2.50.

This small volume contains the papers and resulting discussions which were presented by a Study Group sponsored by the Ciba Foundation. The program was presented in honor of Dr. Y. Zotterman and was held in London in March of 1959. There were 20 participants from Europe and the United States. There are eight papers, both of a review nature and presenting new material. The papers deal with questions of sensory specificity of peripheral nerve endings and of nerve fibers. Methods for recording C fiber conduction are presented and analyses of such recordings are discussed. Problems relative to distinguishing recordings of impulses produced by heat, cold, mechanical stimulation, etc., are discussed and the general con-

clusion was that there are, indeed, specific sensory fibers which react only to nociceptive stimuli. Limitations of technic are responsible for only the most general conclusions.

This small collection of papers is of interest to all neurologists, anatomists, and neurophysiologists. There is sufficient review material present, so that those who are not working in this particular area of endeavor will profit from reading the volume.

Any criticisms would be directed toward the printing which is in quite small type. This has the virtue of producing a pocket-size book but the desirability of saving space and expense is somewhat offset by the discomfort involved in attempting to read it. In a further effort to save space, the discussions are broken and placed in various parts of the volume, when there might have been a half page free of text. Although not a hardship, this feature is a compromise with the ideal. The references for all the papers are placed at the end of the volume and are followed by a subject index. The volume is 120 pages long and contains 41 illustrations.

C. V. B.

*Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions.* 4th Ed. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P. 1079 pages; 24×16 cm. Lea & Febiger, Philadelphia. 1960. Price, \$12.50.

In 1899, Dr. Arthur R. Cushny, then Professor of Pharmacology at the University of Michigan, wrote the first edition of this book. He subsequently returned to Edinburgh and prepared seven revisions before his death in 1926. The next four editions were prepared by Professor C. W. Edmunds of the University of Michigan and Professor J. A. Gunn of Oxford. The thirteenth edition, and the last to bear Cushny's name, was prepared by Dr. Arthur Grollman and Dr. Donald Slaughter for publication in 1947. In 1951 a new series was begun under the authorship of Dr. Grollman; this series is now in its fourth edition.

Since medical texts rarely continue for nearly two thirds of a century, it seems probable that this book as originally conceived was unique in fulfilling a recognized purpose. Cushny sensed this and stated in the preface to the original edition: "My object has been to bridge over the hiatus which exists between the phenomena occurring in the normal organism and those which are elicited in the therapeutic use of drugs, to show how far the clinical effects of remedies may be explained by their action on the normal body, and how these may in turn be correlated with physiological phenomena."

It is impossible for this reviewer to judge how well Cushny's books achieved this objective because of the almost complete turnover of knowledge about drugs and their actions. However, the inference is strong that "Cushny's Pharmacology" gave physicians and students of the early century a new insight into drug action, as expressed by alterations of normal physiology.

How well Dr. Grollman has been able to achieve this objective can only be judged by each user of the current edition. The opinion here is that he nearly succeeds.

Otherwise, this is an obviously excellent textbook of Pharmacology. It is certainly complete and certainly authoritative; it is also well balanced, meticulously edited, and beautifully produced. It will also serve as an excellent reference—for the above reasons plus the fact that all drugs considered are listed by both *common* and *official* names in the 60-page index.

B. W. A.

*The Diabetic's Handbook*. 2nd Ed. By ANTHONY M. SINDONI, JR., M.D., with 18 collaborators. 285 pages; 21 × 14 cm. The Ronald Press Co., New York, N. Y. 1959. Price, \$4.50.

*Diabetic Manual*. 10th Ed. By ELLIOTT P. JOSLIN, M.D., Sc.D. 304 pages; 20.5 × 13.5 cm. Lea & Febiger, Philadelphia. 1959. Price, \$3.75.

The clinical use of new and hypoglycemic agents appears to have stimulated new and revised editions of these manuals. Similarities include, also, detailed sections on insulin administration, dietotherapy, home laboratory testing, a question and answer section, detailed general and specific health and hygiene advice. It is quite possible that a patient, after reading and understanding these volumes, might have more knowledge of his disease than his medical attendants have. Both volumes, therefore, may be of great aid to the physician, especially the intern and resident. Both books point out that diabetic patients need discipline, integrity, optimism, and self-control (Sindoni, p. 134). Neither one precisely points out that their medical attendants need these same virtues. Both are written for the literate patient who can afford to buy the recommended dietary ingredients.

Dr. Sindoni's book has sections by 17 Philadelphia contributors, including a chiropodist, dietitian, dentist, and psychiatrist, in addition to a foreword, prologue, and introduction. He includes no photographs, few illustrations and tables, and little historical background. Exhortation, authoritarianism, and repetition are restrained. Overeating is not presented as a cause of diabetic coma. Alcoholic beverages are discussed candidly with tables of alcoholic and caloric content.

Dr. Joslin's book is the product of a single author and reads, in many areas, as if he is speaking to the patient in the presence of his physician. Personal, anecdotal, repetitive, and historical, the volume is sprinkled with pictures, portraits, tables, graphs, and quotations from biblical and other sources. Overeating is stated to be a cause of diabetic coma. (Confusion, in the mind of the patient, may arise between tetanus antitoxin and tetanus toxoid (p. 253).)

P. F.

*Tumors of the Pancreas* (Atlas of Tumor Pathology Section VII—Fascicles 27 and 28). By VIRGINIA KNEELAND FRANTZ, M.D., Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. 149 pages; 26 × 20 cm. (paper bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences, National Research Council, Washington, D. C. 1959. Price, \$1.50 (for sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.).

Tumors of the pancreas may interrupt health and well being because of size, by predisposing to pancreatitis, by metastasizing to vital areas or by inducing systemic disturbances such as phlebotrombosis or hypoglycemia. Tumors of the pancreas are cause for complaint because of their effect on the pancreas itself or its effect upon contiguous and continuous structures. Tumors of the pancreas may arise in the pancreas proper or in ectopic pancreatic masses. These and other considerations are ably expounded by Dr. Frantz in this, the twenty-seventh fascicle of the Atlas of Tumor Pathology.

In this fascicle, Dr. Frantz having presented a discourse on the anatomy of the pancreas proceeds to discuss various pathologic features of heterotopic pancreas, and pseudocysts, neoplastic cysts, and carcinomas of the exocrine portion of the pancreas.

In following pages, a lucid presentation of tumors of the endocrine elements of the pancreas is offered.

In the section devoted to carcinoma of the pancreas, those who still hold to painless jaundice as an index of pancreatic carcinoma are reminded that pain is now accepted as the most common initial symptom. Without new light being cast, a brief discussion of diagnostic means is given. Duodenal cytology, the biopsy method, and x-ray signs are mentioned.

In the latter portion of this fascicle, the often neglected concept of associated insular and other endocrine tumors is presented.

To this reviewer, the stronger part of this work is that devoted to pancreatic tumors of insular origin. This opinion probably is influenced by personal interest and is not intended as an unfavorable reflection on the sections given to tumors of acinar and ductal origin.

The text and the generous supply of excellent illustrations make this fascicle a worthy addition to any medical or surgical library.

D. L. REIMANN, M.D.

### BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Arthritis and Allied Conditions: A Textbook of Rheumatology.* 6th Ed. Editor: JOSEPH LEE HOLLANDER, M.D.; Section Editors: EDWARD W. BOLAND, M.D., RICHARD H. FREYBERG, M.D., WALLACE GRAHAM, M.D., JOHN LANSBURY, M.D., CURRIER McEWEN, M.D., CHARLES RAGAN, M.D., WILLIAM D. ROBINSON, M.D., and CHARLEY J. SMYTH, M.D. 1,306 pages; 24 × 16 cm. 1960. Lea & Febiger, Philadelphia. Price, \$20.00.

*Attenuated Infection: The Germ Theory in Contemporary Perspective.* By HAROLD J. SIMON, M.D., Ph.D., Assistant Professor in Medical Microbiology and Assistant Professor in Medicine, Stanford University School of Medicine; forewords by RENÉ J. DUBOS, Ph.D., and WALSH McDERMOTT, M.D. 349 pages; 24 × 16 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, \$10.00.

*Body Fluids in Surgery.* 2nd Ed. By A. W. WILKINSON, Ch.M., F.R.C.S.E., F.R.C.S., Nuffield Professor of Paediatric Surgery, The Institute of Child Health of the University of London, etc. 276 pages; 22.5 × 14.5 cm. 1960. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$5.00.

*Classics of Medicine and Surgery* (formerly titled: *Epoch-Making Contributions to Medicine, Surgery and the Allied Sciences*). Collected by C. N. B. CAMAC. 435 pages; 20.5 × 13.5 cm. (paper-bound). Dover edition, first published in 1959, is an unabridged and unaltered republication of the work originally published by W. B. Saunders Company in 1909. Dover Publications, Inc., New York. Price, \$2.25.

*Clinical Physiology. Volume One: Electrolyte Balance, Water Metabolism, Renal Function, Gastro-intestinal Function, Hepatic Failure.* By KATHLEEN E. ROBERTS, M.D., Director of Research, United States Public Health Service Hospital, San Francisco, California, etc. 226 pages; 23.5 × 15.5 cm. 1960. Filmer Publishing Co., San Francisco. Price, \$6.50.

*The Concise Encyclopedia of Modern Surgery.* By JAMES HALE RUTLEDGE, B.S., M.D., F.A.C.S.; illustrated by the author. 308 pages; 27 × 18.5 cm. 1960. Chilton Company—Book Division, Philadelphia. Price, \$8.00.

*Differential Diagnosis of the Electrocardiogram.* By SIDNEY R. ARBEIT, M.D., F.A.C.C., Associate Professor of Clinical Medicine, Seton Hall College of Medicine, Attending Physician, Jersey City Medical Center, etc.; IRA L. RUBIN, M.D., F.A.C.P., F.A.C.C., Lecturer in Medicine, Columbia University, etc.; and HARRY GROSS, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Columbia University, Attending Physician, Medical Division, Montefiore Hospital, New York City, etc. 212 pages; 24.5 × 21 cm. 1960. F. A. Davis Company, Philadelphia. Price, \$10.50.

*Effects of Experimental Alterations of the Thyroid Function on the Adrenal Medulla of the Mouse* (*Acta Endocrinologica, Supplementum 48*). By VÄINÖ K. HOPSU. 87 pages; 24 × 16 cm. (paper-bound). 1960. Periodica, Copenhagen. Price, \$2.55.

*Electrophysiology of the Heart.* By BRIAN F. HOFFMAN, M.D., Associate Professor of Physiology, College of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York; and PAUL F. CRANFIELD, Ph.D., Associate Professor of Physiology, College of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York; with a foreword by FRANKLIN D. JOHNSTON, M.D. 323 pages; 22 × 14.5 cm. 1960. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, \$12.50.

*Epilepsy and Related Disorders* (in two volumes). By WILLIAM GORDON LENNOX, A.B., A.M., M.D., Sc.D. (Hon.), Associate Professor of Neurology, Emeritus, of Harvard University School of Medicine, etc.; with the collaboration of MARGARET A. LENNOX, A. B., M.D., Member, Institute of Neurophysiology, Copenhagen, etc. 1,168 pages (both volumes); 24.5 × 16.5 cm. 1960. Little, Brown and Company, Boston. Price, \$13.50.

*Experiments and Observations on the Gastric Juice and the Physiology of Digestion* (facsimile of the original edition of 1833, together with a biographical essay, *A Pioneer American Physiologist*, by SIR WILLIAM OSLER). By WILLIAM BEAUMONT, M.D., Surgeon in the United States Army. 279 pages; 20.5 × 13.5 cm. (paper-bound). 1959. Dover Publications, Inc., New York. Price, \$1.50.

*The Federal and Provincial Health Services in Canada: A Volume Commemorating the Fiftieth Year of the Canadian Public Health Association and of the Canadian Journal of Public Health, 1910-1959.* Edited by R. D. DEFRIES, C.B.E., M.D., D.P.H., LL.D., DR.P.H., Consultant and Director-Emeritus, Connaught Medical Research Laboratories, University of Toronto. 147 pages; 25.5 × 17 cm. (paper-bound). 1959. Canadian Public Health Association, Toronto. Price, \$1.75.

*Gastric Cytology: Principles, Methods and Results.* By RUDOLF OTTO KARL SCHADE, M.D. (Dunelm), M.D. (Tübingen), L.R.C.P., M.R.C.S., Senior Lecturer, Department of Pathology, Royal Victoria Infirmary, Kings College, University of Durham. 83 pages; 25.5 × 19 cm. 1960. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$8.00.

*The Hawaii Health Survey: Description and Selected Results, Oahu, Hawaii, October 1958-September 1959. The Design, Content, Definitions, and Preliminary Findings of the Health Interview Survey Conducted Coöperatively by the Hawaii State Department of Health, the Oahu Health Council, and the National Health*



- Survey. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584-C3.* 54 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, at 40¢.
- The Head, Neck, and Trunk: Muscles and Motor Points.* 2nd Ed. By DANIEL P. QUIRING, Ph.D., Late Head of the Anatomy Division, Cleveland Clinic Foundation and Associate Professor of Biology, Western Reserve University; Second Edition, Revised and Edited by JOHN H. WARFEL, Ph.D., Assistant Professor of Anatomy, The University of Buffalo, School of Medicine, Buffalo, New York. 124 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, \$3.25.
- The Human Lung.* By HEINRICH VON HAYEK, M.D., Ph.D., Professor and Head of the Institute of Anatomy at the University of Vienna; revised and augmented by the author; translated by VERNON E. KRAHL, Ph.D., Professor of Anatomy, Department of Anatomy, School of Medicine, University of Maryland, Baltimore, Maryland. 372 pages; 25.5 × 17 cm. 1960. Hafner Publishing Company, Inc., New York. Price, \$13.50.
- Leukaemia: Research and Clinical Practice.* By F. G. J. HAYHOE, M.A., M.D. (Cantab.), M.R.C.P. (Lond.), Lecturer in Medicine, University of Cambridge, etc. 335 pages; 25.5 × 19.5 cm. 1960. Little, Brown and Company, Boston. Price, \$16.00.
- Neuropharmacology: Transactions of the Fifth Conference, May 27, 28, and 29, 1959, Princeton, N. J.* Edited by HAROLD A. ABRAMSON, M.D., Research Psychiatrist, The Biological Laboratory, Cold Spring Harbor, etc. 251 pages; 24 × 16 cm. 1960. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$6.00.
- The Office Assistant in Medical Practice.* 2nd Ed. By PORTIA M. FREDERICK, Instructor, Medical Office Assisting, Long Beach City College; and CAROL TOWNER, Director of Special Services, Communications Division, American Medical Association. 407 pages; 21 × 15 cm. 1960. W. B. Saunders Company, Philadelphia. Price, \$5.25.
- Peptic Ulcers Reported in Interviews, United States, July 1957-June 1959. Statistics on Prevalence of Peptic Ulcers and Associated Disability by Age, Sex, and Medical Care Status. Based on Data Collected in Household Interviews During the Period July 1957-June 1959. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584-B17.* 26 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢.
- Psychophysiological Approach in Medical Practice.* By WILLIAM W. SCHOTTSTAEDT, M.D., Associate Professor, Department of Preventive Medicine and Public Health, Department of Medicine, and Department of Psychiatry, Neurology and and the Behavioral Sciences, The University of Oklahoma Medical Center. 352 pages; 23.5 × 15 cm. 1960. The Year Book Publishers, Inc., Chicago. Price, \$8.00.
- Recent Advances in Biological Psychiatry, Including a Havelock Ellis Centenary Symposium on Sexual Behavior. The Proceedings of the Fourteenth Annual Convention and Scientific Program of the Society of Biological Psychiatry, Atlantic City, June 1959.* Edited by JOSEPH WORTIS, M.D., Associate Clinical

Professor of Psychiatry, State University of New York, Downstate Medical College, Brooklyn, New York. 417 pages; 23.5 × 15.5 cm. 1960. Grune & Stratton, New York. Price, \$13.50.

*Source Book of Medical History.* Compiled with notes by LOGAN CLENDENING, M.D. 685 pages; 20.5 × 13.5 cm. (paper-bound). New Dover edition, first published in 1960, is an unabridged and unaltered republication of the work first published in 1942. Dover Publications, Inc., New York. Price, \$2.75.

*Teacher Preparation for Health Education: Report of a Joint WHO/UNESCO Expert Committee. World Health Organization of Technical Report Series No. 193.* 19 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

*Thoracic Surgery Before the 20th Century.* By LEW A. HOCHBERG, B.S., M.A., M.D., C.M., F.A.C.S., F.C.C.P. and F.A.C.C., Consultant Thoracic Surgeon Lutheran and Sea View Hospitals, etc.; with a foreword by EDWARD D. CHURCHILL, M.D. 858 pages; 23.5 × 16 cm. 1960. Vantage Press, New York. Price, \$15.00.

*The Thyroid-Vitamin Approach to Cholesterol Atheromatosis and Chronic Disease: A Ten-Year Study.* By MURRAY ISRAEL, M.D.; with a foreword by HENRY L. RUSSEK, M.D. 132 pages; 23 × 15.5 cm. (paper-bound). 1960. Vascular Research Foundation, New York. Price, \$1.00.

*Transactions of the New England Surgical Society: Fortieth Annual Meeting, Portsmouth, New Hampshire, October 16 and 17, 1959. Volume XL, for the Year 1959.* 216 pages; 22.5 × 15 cm. (paper-bound). 1960. The New England Journal of Medicine, Boston. Price, \$2.00.

*Tumors of the Female Sex Organs. Part 2: Tumors of the Vulva, Vagina and Uterus. (Atlas of Tumor Pathology, Section IX—Fascicle 33.)* By ARTHUR T. HERTIG, M.D., Shattuck Professor of Pathological Anatomy, Harvard Medical School, Boston, Massachusetts, etc.; and HAZEL GORE, M.B., B.S., Associate in Pathology, Harvard Medical School, Boston, Massachusetts, etc. 275 pages; 26 × 20 cm. (paper-bound). 1960. Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C., at \$2.50.

*Viral Infections of Infancy and Childhood: A Symposium of the Section on Microbiology, The New York Academy of Medicine. (No. 10.)* Edited by HARRY M. ROSE, M.D., John E. Borne Professor of Medical and Surgical Research, College of Physicians and Surgeons, Columbia University. 244 pages; 23.5 × 15.5 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. Price, \$8.00.

## MEDICAL NEWS

### ERRATUM

In the July issue of the *ANNALS OF INTERNAL MEDICINE*, in this section on "Medical News," announcement was made of an International Symposium on the Etiology of Myocardial Infarction which, it was stated, would occur in November, 1960. The date mentioned is in error. This meeting is scheduled for November 16-18, 1961, not 1960.

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### AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS

It was voted at the April meeting of the Board of Regents in San Francisco on the recommendation of the Committee on Fellowships and Scholarships to approve a change in Research Fellowships given by the College. There will be no one-year College Research Fellowships other than those already awarded last November for the academic year July 1, 1960 to June 30, 1961. It is believed that a much greater contribution will be made by the College with the establishment of three-year Research Fellowships, although for the time being the total number of fellowships will be relatively few. Applications may be received, however, for two Research Fellowships to be awarded for a term of three years.

The purpose of such three-year fellowships shall be stated as that of further developing in young physicians a major interest in research in any science basic to medicine or in medical education, or both. Furthermore, it is to be stipulated that the recipient of such a fellowship shall devote a minimum of 80 per cent of his time to research, regardless of the type of appointment that he holds in any given institution.

Applications for the recipients of such fellowships shall be made by the Chairman of the Department of Medicine in any institution in the United States and Canada with a recognized program of medical education and research. The Chairman of the Department of Medicine in any such institution shall be responsible for presenting a careful and complete evaluation of any such individual whom he wishes to recommend for such a College Fellowship. Such recommendation shall be further implemented by a letter from the Governor of the State or Province concerned. Not more than one name may be recommended by any Chairman of a Department of Medicine in any given institution in any calendar year.

Applications for such Research Fellowships may be made only on behalf of physicians who are citizens of the United States or Canada and who have completed an internship in an approved hospital and have had at least two years of approved residency training, preferably with a third year of residency or a year of research training.

The Chairman of the Department who sponsors a given applicant must be prepared to provide adequate facilities for the recipient of this fellowship during the course of his fellowship, or to help him to obtain such facilities in an institution in which research is to be carried out. If the recipient is to carry on his research in an institution other than the one from which the initial application is made, the grant for such work elsewhere will follow the recipient.

Such research grants will be made by the College to start on July 1 of any given year, unless for satisfactory reasons a necessary and proper delay is requested.

On March 1 of the first and second calendar years following the grant of a research fellowship a report of progress shall be required from the recipient of the award and from the Chairman of the Department who made the original application

and recommendation. Renewal of the grant at the end of the first and second twelve-month periods will be contingent upon the receipt of reports of progress satisfactory to the Committee on Fellowships and Scholarships. A final report at the end of the third year of fellowship will also be required from the recipient and from his preceptor.

For further information write

Edward C. Rosenow, Jr., M.D.  
Executive Director  
American College of Physicians  
4200 Pine Street  
Philadelphia 4, Pa.

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#### AMERICAN COLLEGE OF PHYSICIANS SCHOLARSHIPS

##### *Mead Johnson Residency Scholarships*

These scholarships are designed to aid deserving young physicians planning careers in the specialty of internal medicine and are financed by Mead Johnson & Company.

The nominee must be in his internship or residency period, with some preference to residents. He must intend to practice internal medicine. He must appear to possess attributes for success in the practice of internal medicine. He must need funds to attain his goal of adequate education in internal medicine.

Ten such awards are made annually. The stipend for each is \$1,000.00. Applications must be filed with the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa., not later than October 1 each year. Selections will be made at the mid-November meeting of the Board of Regents, and scholarships begin the following July 1.

##### *Traveling Scholarships*

The aim of these scholarships is to provide an opportunity for worthy, young physicians, preferably Associates of the College, to spend a month, more or less, as visiting fellows at some institution, or institutions, for observation and postgraduate study. The Committee on Fellowships and Scholarships of the College facilitates opportunities for these scholarships at outstanding institutions where a month's observation, contact and study will be an exceptional inspiration and a practical source of training. The income, approximately \$400.00 each, is used for payment of travel expenses, in whole or in part. Recipients are chosen and institutions designated by the Committee on Fellowships and Scholarships, subject to approval by the Board of Regents.

##### *The A. Blaine Brower Traveling Scholarships:*

There are two of these fellowships, the first having been initiated through a grant by Dr. A. Blaine Brower, F.A.C.P., of Dayton, Ohio; the second A. Blaine Brower Traveling Scholarship was added by the Board of Regents.

##### *The Elizabeth Archbold Bowes Traveling Scholarship:*

The first scholarship, established through an annual grant by Mrs. Margaret Bowes Murphy, Chicago, Ill., in memory of her mother, and administered on the same basis as the Brower Traveling Scholarships. However, the Bowes Traveling Scholarship is restricted to candidates from Canada.

##### *The Willard O. Thompson Memorial Traveling Scholarship:*

First annual scholarship, established by the late Dr. Thompson's widow, Dr. Phebe Thompson, and by friends of Dr. Thompson. It is particularly directed toward

the field of endocrinology, the specialty in which Dr. Thompson was most interested. It is administered on the same bases as the Brower Traveling Scholarships.

Interested Associates of the College shall file application on or before October 15 each year; recipients will be selected by the Committee on Fellowships and Scholarships and the Board of Regents at their mid-November meeting. Scholarships will be arranged to start after the following January 1, at the convenience of the recipient and of the preceptor or institution.

Applications may be obtained from the Executive Director of the College.

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#### NATIONAL TUBERCULOSIS ASSOCIATION FELLOWSHIPS

The Medical Section of the National Tuberculosis Association, the American Thoracic Society provides fellowships and traineeships for the graduate education of investigators and teachers in the field of respiratory diseases and tuberculosis.

Applications must be submitted by November 1st. Further information about fellowships may be obtained upon request from:

Director of Medical Education,  
American Thoracic Society,  
1790 Broadway,  
New York 19, N. Y.

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#### THE GLORNEY-RAISBECK FELLOWSHIP

The New York Academy of Medicine has announced that the Glorney-Raisbeck Fellowship in the Medical Sciences will be awarded for one year of research or study in any field of medicine or its allied sciences. The initial award will be for the academic year beginning July 1, 1961. The fellowship is renewable on a year-to-year basis for two additional years. It carries a stipend of \$5,000 and is open only to M.D.'s who have "demonstrated potential for productivity in research and teaching." Candidates must assure the Committee on Medical Education of an institution in which to carry on their projects. For information contact Dr. Aims C. McGuinness, Executive Secretary, Committee on Medical Education, The New York Academy of Medicine, 2 E. 103 St., New York 29, N. Y.

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#### EXAMINATIONS AND LICENSURE

*American Board of Pediatrics*: Written, New York City, January, 1961. Final date on filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

*American Board of Psychiatry and Neurology*: New York, New York, Dec. 12-13. Child Psychiatry, Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

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#### FUTURE MEETINGS

Sept. 1-7—International Congress of Nutrition at Washington, D. C. Dr. Milton O. Lee, 9650 Wisconsin Ave., Washington 14, D. C., General Secretary.

Sept. 4-10—International Society of Hematology, Tokyo, Japan. Dr. James L. Tullis, Suite 6 D, 1180 Beacon St., Brookline 46, Mass., Secretary-General, Western Hemisphere.

Sept. 7-10—Medical Women's International Association at Baden-Baden, Germany. Dr. Grete Albracht, Heilwigstr. 12, Hamburg 20, Germany, President.

Sept. 12-15—International Society of Blood Transfusion at Tokyo, Japan. Headquarters: Nihon Toshi Center, Hirakawacho, Chiyoda-Ku. Dr. Seizo Murakami,

- Blood Transfusion Research Laboratory, Japanese Red Cross Society, Shibuya, Tokyo, Secretary-General.
- Sept. 13-15—The Fourth National Cancer Conference of the American Cancer Society and the National Cancer Institute at Minneapolis, Minn. Coordinator: Roald N. Grant, M.D., American Cancer Society, Inc., Medical Affairs Department, 525 West 57th Street, New York 1, N. Y.
- Sept. 15-22—World Medical Association, at West Berlin, Germany. Headquarters: Berlin-Hilton Hotel. Dr. Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y., Executive Secretary.
- Sept. 18-21—International Meeting of Forensic Pathology, New York City. Dr. Milton Helpert, 55 E. End Avenue, New York 28, N. Y.
- Sept. 22-26—International Cancer Cytology Conference, Madrid, Spain. Miss Elizabeth L. Hughes, 3007 Salzedo, Coral Gables, Fla., Corresponding Secretary.
- Sept. 29-Oct. 1—Fourth Scientific Meeting of the Society of Social Medicine at Oxford, England. Headquarters: Oxford University. Dr. Alice M. Stewart, Department of Social Medicine, 8, Keble Road, Oxford, England, Secretary.
- October 2-4—First International Symposium of Cybernetic Medicine at Naples, Italy. Professor Renato Vinciguerra, Via Roma, 348-Naples, Italy, S.I.M.C. Secretary.
- Oct. 5-8—American Academy for Cerebral Palsy, Pittsburgh, Pa. Headquarters: Penn-Sheraton Hotel. Dr. Joseph D. Russ, 1520 Louisiana Ave., New Orleans 15, La., Executive Secretary.
- Oct. 11-12—Congress on Industrial Health at Charlotte, N. C. Headquarters: Hotel Charlotte. Council on Occupational Health, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.
- Oct. 13-15—Academy of Psychosomatic Medicine, at Philadelphia, Pa. Headquarters: Benjamin Franklin Hotel. Dr. Mertram B. Moss, 55 E. Washington, Chicago 2, Ill.
- Oct. 21-25—American Heart Association, Inc., at St. Louis, Mo. Headquarters: Jefferson Hotel. Mr. Rome A. Betts, 44 E. 23rd St., New York 10, N. Y., Executive Director.
- Oct. 23-29—The Seventh Panamerican Congress of Gastroenterology in Santiago, Chile. Congress Office, Dr. Ricardo Katz, Hospital del Salvador, Casillar 70-D, Santiago, Chile.
- Oct. 26-27—Industrial Hygiene Foundation of America, Inc., at Pittsburgh, Pa. Headquarters: Mellon Institute. Dr. H. H. Schrenk, 4400 Fifth Ave., Pittsburgh 13, Pa., Managing Director.
- Oct. 31-Nov. 3—Interstate Postgraduate Medical Association of North America at Pittsburgh, Pa. Headquarters: Pittsburgh-Hilton Hotel. Mr. Roy T. Ragatz, Box 1109, Madison 1, Wis., Executive Director.
- Oct. 31-Nov. 2—Association of American Medical Colleges at Hollywood Beach, Fla. Headquarters: Diplomat Hotel. Dr. Ward Darley, 2530 Ridge Ave., Evanston, Ill., Executive Director.
- Nov. 2-5—American Society of Tropical Medicine and Hygiene at Los Angeles, Calif. Headquarters: Biltmore Hotel. Dr. Rolla B. Hill, 3575 St. Gaudens Rd., Miami 33, Fla., Executive Secretary.
- Nov. 29-Dec. 2—The American Medical Association Clinical Meeting at Washington, D. C.
- Nov. 30-Dec. 3—Canadian Heart Association and National Heart Foundation of Canada, Joint Annual Meeting at Toronto, Ont., Canada. Headquarters: Royal York Hotel. Dr. John B. Armstrong, National Heart Foundation, 501 Yonge St., Toronto 5, Canada.
- Dec. 4-9—Radiological Society of North America at Cincinnati, Ohio. Headquarters: Netherland Hilton Hotel. Dr. Donald S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Secretary.



## POSTGRADUATE EDUCATION

- Oct. 3-5, 1960—Diabetes Mellitus in Relation to General Medicine. By Alexander Marble, M.D., and Associates at the New England Deaconess Hospital. Tuition: \$30.00.
- Oct. 3, 1960 to Mar. 31, 1961—Pediatrics. By R. Cannon Eley, M.D., and Associates at Children's Hospital Medical Center. Tuition: \$750.00. For catalogue and form of application, write to: Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.
- Oct. 3-May 31, 1961—Cardiovascular Disease. Harvard Medical School, Boston, Mass. Fee: \$800. For information contact Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.
- Oct. 10-14—A.C.P. Course: Cancer and the Internist—1960 Concepts: Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N. Y.; Rulon W. Rawson, M.D., F.A.C.P., Director.
- Oct. to Dec., 1960 (8 consecutive Wednesdays—Oct. 19 to Dec. 7).—Recent Advances in Medicine. Temple University Medical Center, Philadelphia, Pa.; 11:00 A.M. to 4:00 P.M. Registration fee: \$50.00. For further information and curriculum, write to Dr. Albert J. Finestone, Director, Postgraduate Course, Department of Medicine, Temple University Hospital, Philadelphia 40, Pa.
- Oct. 27-29—Postgraduate Gastroenterology, at Philadelphia, Pa. Headquarters: Bellevue-Stratford Hotel. For information contact American College of Gastroenterology, 33 West 60th St., New York, 23, N. Y.

*Department of Health, Education, and Welfare**Communicable Disease Center**Atlanta 22, Georgia*

## Schedule of Laboratory Refresher Training Courses

October 1960—June 1961

Dates	Courses	Duration
Oct. 10-21	Fundamentals of Virology (819)	2 wks.
Oct. 31-Nov. 11	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2 wks.
Nov. 28-Dec. 2	Laboratory Methods in the Diagnosis of Rabies (826)	1 wk.
Dec. 5-9	Bacteriophage Typing of Staphylococci (856)	1 wk.
Jan. 9-Feb. 3	Laboratory Methods in Medical Mycology (815)	4 wks.
Jan. 23-Feb. 10	Serologic Methods in Microbiology (941)	3 wks.
Jan. 30-Feb. 10	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2 wks.
Feb. 13-24	Laboratory Methods in the Study of Pulmonary Mycoses (817)	2 wks.
Feb. 27-Mar. 17	Laboratory Methods in Medical Bacteriology (838)	3 wks.
Mar. 6-10	Laboratory Diagnostic Methods in Veterinary Mycology (940)	1 wk.
Mar. 13-31	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases (820)	3 wks.
Mar. 20-24	Special Problems in Medical Bacteriology (839)	1 wk.
Mar. 27-Apr. 7	Laboratory Methods in Enteric Bacteriology (850)	2 wks.

Apr. 3-7	Laboratory Methods in the Diagnosis of Rabies (826)	1 wk.
**	Laboratory Methods in the Diagnosis of Malaria (805)	1 wk.
**	Special Training in Virus Techniques (821)	2-4 wks.
**	Typing of <i>Corynebacterium diphtheriae</i> (842)	1 wk.
**	Special Problems in Enteric Bacteriology (851)	2 wks.
**	Phage Typing of <i>Salmonella typhosa</i> (852)	1 wk.
**	Laboratory Methods in the Diagnosis of Leptospirosis (853)	1-4 wks.
**	Serologic Differentiation of Streptococci (854)	2 wks.
**	Special Problems in Microbiology (942)	1-2 wks.

\*\* Courses given by special arrangement only.

Nov. 28-Dec. 2—Coronary Artery Disease at the Texas Medical Center, Houston, Texas. \$5.00 registration fee for those desiring AAGP Category I credit. For information contact Dean, The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Bldg., Texas Medical Center, Houston 25, Texas.

The Frederick Rice Lummis Medical Foundation is sponsoring a one day Symposium on Pulmonary Disease to be held on Saturday, October 22, 1960, in the Jesse Jones Library Building Auditorium in Houston, Texas. The condensed program is as follows:

Morning Session:

8:30 a.m.	Registration
9:00 a.m.	The Diagnostic Approach to Diffuse Pulmonary Disease, Maurice S. Segal, M.D., Clinical Professor of Medicine, Tufts University School of Medicine, Director Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital, Boston, Mass.
9:45 a.m.	Carcinoma of the Lung, Differential Diagnosis, H. Corwin Hinshaw, M.D., Clinical Professor of Medicine and Head of Division, Diseases of the Chest, Stanford University School of Medicine, San Francisco, California.
10:30 a.m.	Cor Pulmonale, John B. Hickham, M.D., Professor of Medicine and Chairman, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana.
11:15 a.m.	Physiologic Diagnosis of Emphysema, Joel E. Reed, M.D., Diagnostic Clinic of Houston; Clinical Assistant Professor of Medicine, Baylor University College of Medicine, Houston, Texas.
12:00 Noon	Lunch
1:30 p.m.	Some Observations on the Effect of Oxygen in Health and Disease, John B. Hickham, M.D.
2:15 p.m.	Differential Diagnosis of Mediastinal Disorders, H. Corwin Hinshaw, M.D.
3:00 p.m.	The Current Status of Inhalation Therapy in Various Pulmonary Disorders, Maurice S. Segal, M.D.
3:45 p.m.	Clinical Pathologic Conference—Pulmonary Problem Presented by: Thomas G. Vandivier, M.D. Moderator: William M. Donohue, M.D. Discussants: John B. Hickham, M.D. H. Corwin Hinshaw, M.D. Maurice S. Segal, M.D. Pathologist: William T. Hill, M.D. Radiologist: John M. Phillips, M.D.

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The author<sup>2</sup> recommends that this therapy be continued for a minimum of five to six months if the pseudopregnancy is being effected to avoid operation. The side effect of nausea, which usually disappears within four or five days, may be diminished by starting with 5 mg. instead of 10 mg. of Enovid, by use of an antiemetic or by administering the drug with the evening meal or with milk or an antacid.

**How Supplied:** Enovid (brand of norethynodrel with ethynylestradiol 3-methyl ether) is supplied as uncoated, scored, coral-colored tablets of 10 mg. each.

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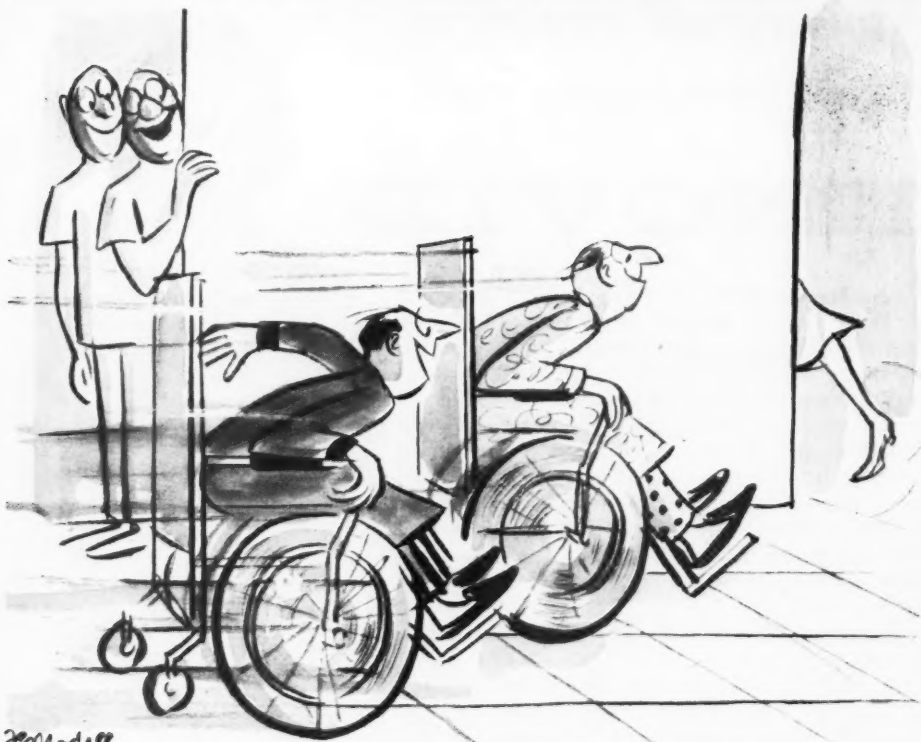
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1. Andrews, M. C.; Andrews, W. C., and Strauss, A. F.: Effects of Progestin-Induced Pseudopregnancy on Endometriosis: Clinical and Microscopic Studies, *Am. J. Obst. & Gynec.* 78:776 (Oct.) 1959.

2. Kistner, R. W.: Endometriosis and Infertility, *Clin. Obst. & Gynec.* 2:877 (Sept.) 1959.

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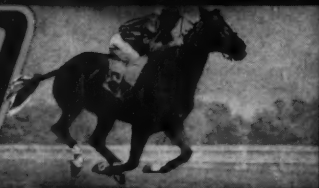
## References:

1. Segal, M. S., and Ouliano, M. J. *Chronic Pulmonary Emphysema*, New York, Grune & Stratton, 1953, p. 99. 2. Farber, S. M., and Wilson, R. H. *L.A. Ann. Int. Med.* 50:1241, 1959. 3. Barach, A. L., and Cromwell, H. A. *Mod. Clin. No. America*, May 1940, p. 621. 4. Bickerman, H. A., and Barach, A. L. *Drugs in Choice*, 1960-1961 (4th Month, 63 J.), St. Louis, The C. V. Mosby Co., 1960, p. 524.

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**ADMINISTRATION AND DOSAGE:** Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

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**SIDE EFFECTS:** In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, **DIABINESE** should be discontinued.

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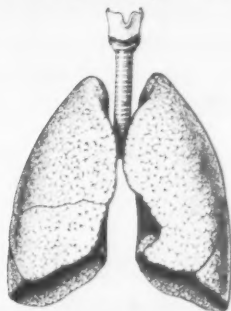


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## performance in “complicated” cases

“Extra” activity, milligram for milligram<sup>2-4</sup> is the basis for outstanding clinical performance. Results of DECLOMYCIN therapy were satisfactory in a series of pneumonia cases, over half of which were complicated by pleural, suppurative, bronchial, or underlying structural lung problems.<sup>1</sup>



1. Duke, C. J.; Katz, S., and Donohoe, R. F.: Demethylchlortetracycline in the Treatment of Pneumonia, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline, Read at Seventh Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A., and Finland, M.:

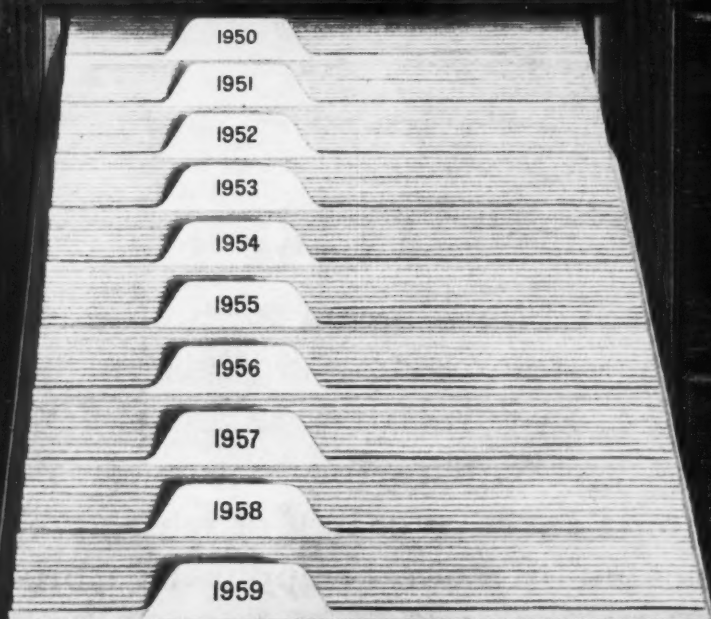
Antibacterial Activity of Serum of Normal Subjects After Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. *New England J. Med.* 260:1099 (May 28) 1959. 4. Lichter, E. A.; Sobel, S.; Spies, H. W.; Lepper, M. H. and Dowling, H. F.: Demethylchlortetracycline Therapy in Pneumonia, Scarlet Fever and Other Infections. *A.M.A. Arch. Int. Med.* 105:601 (Apr.) 1960.

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FULL ACTIVITY . . . LESS ANTIBIOTIC . . . SUSTAINED-PEAK CONTROL . . . “EXTRA-DAY” PROTECTION AGAINST RELAPSE

PRECAUTIONS: The use of antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential.

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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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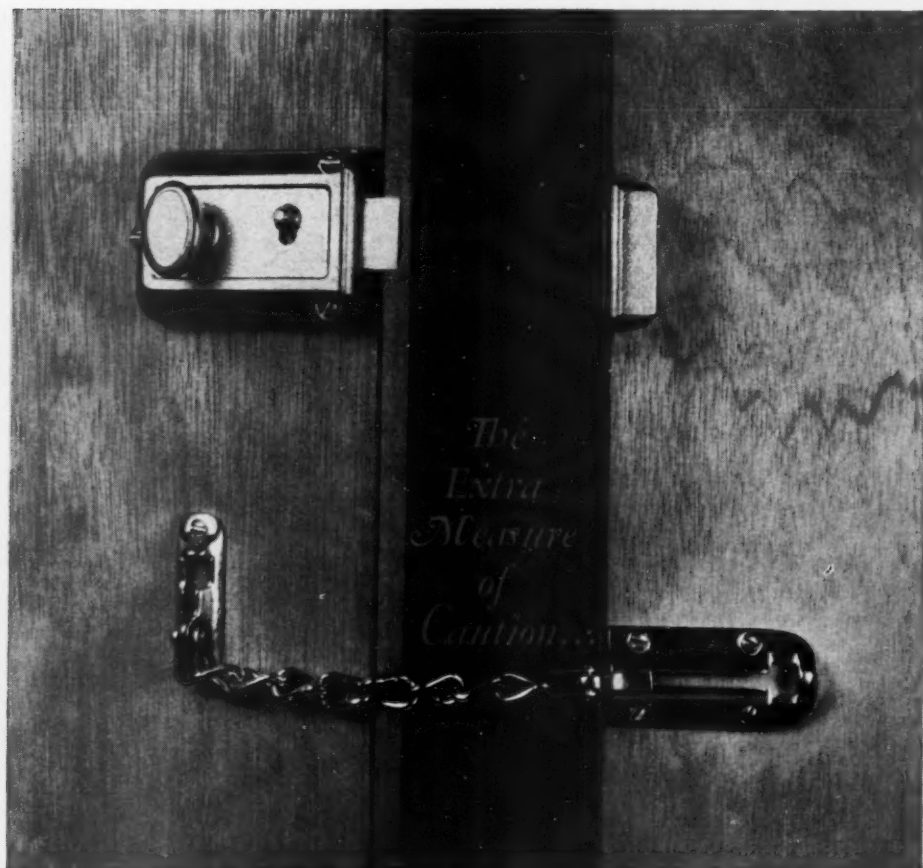
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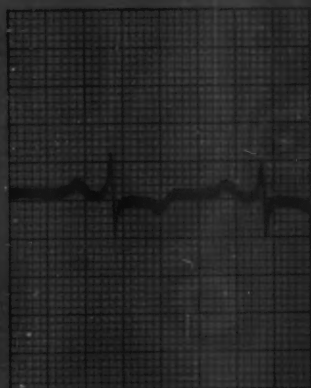
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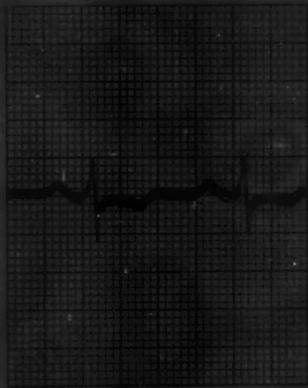
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#### References:

1. Alfaro, E. D.; Graesslin, V. and Schloster, E.: Michigan Acad. Gen. Pract. Detroit, November, 1959. 2. Hosh, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Horvitz, E.: Personal communication, 1959. 4. Spelman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 5. Bowers, E.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Devina, L. J.: *Exper. Med. & Surg.* in press. 7. Scoville, J. E.: Personal communication, 1959. 8. Kroetz and Biorch: Personal communication, 1959.

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**SUPPLIED** 5 cc. color-break ampules, boxes of 10

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capsules for oral use...fine aqueous dispersion for parenteral administration.

***Compatibility***

unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.

***Low dosage forms***

no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

Capsules—5 mg; Ampuls—1 mg/0.5 cc

# STOP BLEEDING

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey



Each tablet contains:

Provera (medroxyprogesterone acetate) 2.5 mg.  
 Cardrase (ethoxzolamide) ..... 35 mg.  
 Levanil (ectylurea) ..... 300 mg.

DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days before the period.

THE UPJOHN COMPANY / KALAMAZOO, MICHIGAN

# CYTRAN

## GETS AT THE CAUSE

### to restore hormonal balance...

*corrective therapy* Because Cytran contains the new progestin, Provera,<sup>†</sup> you can now reach the *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

### to comfort the patient...

*symptomatic therapy* An effective diuretic (Cardrase<sup>†</sup>) and a mild tranquilizer (Levanil<sup>†</sup>) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.

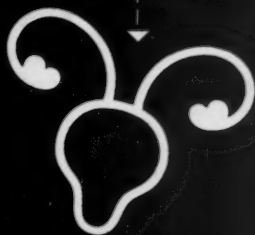


\*TRADEMARK

†TRADEMARK, REG. U. S. PAT. OFF.

**Upjohn**

# OF PREMENSTRUAL TENSION



## AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE

### *In what type of patient is urinary tract infection up to four times more common than in others?*

The diabetic. Incidence of infections of the urinary tract in diabetes ranges from 12 to 20 per cent as compared to about 4.5 per cent for the rest of the population.

Source: Peters, B. J.: J. Michigan M. Soc. 57:1419, 1958.



"In the presence of urinary infection the determination [of pH] is of the utmost utility. Often therapy is guided as much by the reaction of the urine as by the more detailed bacteriologic studies."<sup>1</sup>

The detection of protein and the detection of sugar in the urine are two of the most commonly performed and diagnostically important tests in all types of medical practice.<sup>2</sup>

**NOW... check urine reaction routinely—  
3 test results in 10 seconds**

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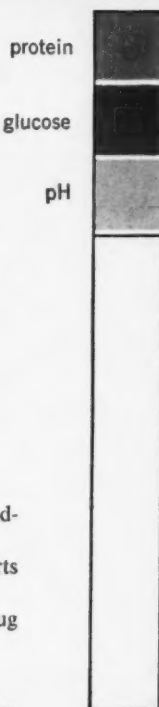
BRAND Reagent Strips

Colorimetric combination test for urinary  
*pH, protein and glucose*

- colorimetric readings eliminate guesswork... 3 standardized color charts provided
- only drops of urine required... no more Q.N.S. reports
- completely disposable... no "cleanup"
- no false positives from turbidity interference, drug metabolites or other urinary constituents

Supplied: COMBISTIX Reagent Strips—Bottles of 125.


(1) Williamson, P.: Practical Use of the Office Laboratory and X-Ray, Including the Electrocardiograph. St. Louis, C. V. Mosby Company, 1957, p. 41. (2) Free, A. H., and Fonner, D. E.: Studies With a Combination Test for Detection of Glucose and Protein, Abstract of 133rd Meeting, American Chemical Society, San Francisco, April 13-18, 1958, pp. 14c-15c.







in peripheral vascular disease...  
brings blood to deep tissues  
without troublesome  
gastrointestinal side effects<sup>1</sup>

myo--vascular relaxant

**VASODILAN<sup>®</sup>**

Isosuprine hydrochloride, Mead Johnson

- increases blood flow by direct action on the smooth muscle of the blood vessels<sup>1,2</sup>
- provides relief in a high percentage of patients with a wide variety of peripheral vascular disorders<sup>1-7</sup>
- effective in intermittent claudication,<sup>2,3</sup> coldness and numbness of extremities,<sup>4,5</sup> trophic ulcers,<sup>5,6</sup> and leg cramps<sup>5,7</sup> associated with arteriosclerosis obliterans, diabetic vascular disease, Buerger's disease, Raynaud's disease and frostbite

Dosage and administration: 1 or 2 tablets (10 to 20 mg.) three or four times daily.

Supply: 10 mg. tablets, bottles of 100; 2 cc. ampuls (5 mg./cc.) for intramuscular use, boxes of 8.

References: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shafiel, H.: *Angiology* 10:185-192 (Aug.) 1959. (2) Samuels, S. S., and Shafiel, H. E.: *J.A.M.A.* 177: 142-144 (Sept. 12) 1959. (3) Kraucher, G.: *Prakt. Arzt* 11:325-329, 1957. (4) Birkmayer, W., and Mentastl, M.: *Wien. med. Wchnschr.* 108:395-396 (May 3) 1958. (5) Clarkson, I., and LePere, D.: Detailed report in Mead Johnson research files. (6) Billiotet, J., and Ferrand, J.: *Sem. méd.* 34:635-637 (May) 1958. (7) Singer, R.: *Wien. med. Wchnschr.* 107:734-736 (Sept.) 1957.



**Mead Johnson**  
Symbol of service in medicine

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for patients who act like restless tigers at night



*gentle relaxant-sedative*

WITH TIMED-RELEASE ACTION  
FOR A FULL NIGHT'S SLEEP

# nebralin<sup>®</sup>

TIMED-RELEASE TABLET

Might as well try to put a tiger to bed (and keep him there) as to get most patients to sleep naturally all night. For disturbed, interrupted sleep is the most common sleep problem in routine practice. NEBRALIN — a timed-release tablet — encourages muscular relaxation and sustained, relaxed sleep. The combination of mephenesin and Dorsital\* in NEBRALIN not only relaxes skeletal muscles, overcomes "fatigue-tension" and conditions the body for sleep, but also induces sound, relaxed sleep by gentle CNS sedation. Mephenesin is capable of producing sleep,<sup>1</sup> and when combined with a barbiturate enhances barbiturate action.<sup>2,3</sup> Moreover, the integrated action of the two components permits smaller dosage of each.<sup>4</sup> Thus, NEBRALIN—a gentle relaxant-sedative—avoids morning hangover, *and carries your patients through the middle of the night, especially those patients who complain about waking up at 2 A.M.*

1. Schlesinger, E. B.: Tr. New York Acad. Sc. 2:6 (Nov.) 1948. 2. Richards, R. K., and Taylor, J. D.: Anesthesiology 17:414, 1956. 3. Shideman, F. E.: Postgrad. Med. 24:207, 1958. 4. Berger, F.: Pharmacol. Rev. 1:243, 1949.



Each Nebralin timed-release tablet contains: Dorsital\*, 90 mg.; Mephenesin, 425 mg. **Dosage:** One or two tablets  $\frac{1}{2}$  hour before retiring. **Supplied:** Bottles of 50 Nebralin timed-release Tablets.

\* Dorsey brand of pentobarbital.

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# ENCOURAGING NEWS IN ANGINAL THERAPY

*Reporting on extensive clinical trial of ISORDIL,  
a group of important investigators found  
"impressive improvement in 67% of patients...,"  
favorable response in a total of 75%.*

**1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A. C.**

In their thoroughly documented report on 60 angina patients studied by open clinical trial, Fisch, Boyle, Sperber, and DeGraff found improvement in 75% of patients; 18% did not respond. Minor side reactions (mostly headache) hindered evaluation in only 7% of the patients treated.

## **Average Dosage Low, but Individualization Required**

Average effective dose of ISORDIL was 10 mg. q.i.d.; 26% of patients received higher doses, 16% lower doses. Of all patients, 87% received and tolerated 5 to 15 mg. q.i.d.

## **Headache Commonest Side Effect, Easily Relieved**

Although headache occurred initially in 27% of patients studied, it caused discontinuance of ISORDIL in only 4 patients. Continued therapy, adjustment of dosage, or use of acetylsalicylic acid relieved headache in all other cases.

## **Other Studies Confirm Results, Establish Additional Benefits**

Maintenance of active coronary vasodilation by ISORDIL, as shown by Leslie,<sup>2</sup> Albert<sup>3</sup> and Fremont,<sup>4</sup> virtually eliminates periods of unprotection. Benefits are apparent as early as 15 minutes, persist for at least 4 hours. No lag in onset . . . important during early morning and postprandial stress.

**References:** 1. Fisch, S., Boyle, A., Sperber, R., and DeGraff, A.C.: Presented at the annual meeting of the American Therapeutic Society, Miami Beach, Florida, June 10, 1960. To be published. 2. Leslie, R.: Submitted for publication. 3. Albert, A.: In Manuscript. 4. Fremont, R.E.: To be published.

# ISORDIL®

Isosorbide Dinitrate, Ives-Cameron



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# DEXAMYL® SPANSULE®

brand of dextro amphetamine and amobarbital

brand of sustained release capsules

*to improve mood and restore drive in the nervous, depressed patient*



Caldwell and Nowers<sup>1</sup> state: "The particularly desirable results achieved in depressed, tense, 'nervous' women suggest that, for some patients, ['Dexamyl'] may be more appropriate than the widely used tranquilizers which create an attitude of indifferent calm." These investigators add that 'Dexamyl' "seems to enhance initiative at the same time that it lessens tension, thereby producing a mental attitude which enables the patient to face up to and act upon her problems."

Patients find the 'Spansule' capsule form especially convenient, because they needn't carry medication with them during the day. 'Spansule' capsules also assure fewer forgotten doses, since only one capsule taken in the morning gives 10- to 12-hour therapeutic effect.

'Dexamyl' *Spansule* capsules are available in two strengths, No. 2 (standard strength) and No. 1 (lower strength).

1. Caldwell, W.G., and Nowers, W.: *California Med.* 48:380 (May) 1958.

*leaders in psychopharmaceutical research*

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# Lifts depression...



**Your patient responds within a few days.** Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety calmed — *often in two or three days.* He eats properly, sleeps well, and his depression no longer complicates your basic regimen.



# as it calms anxiety!

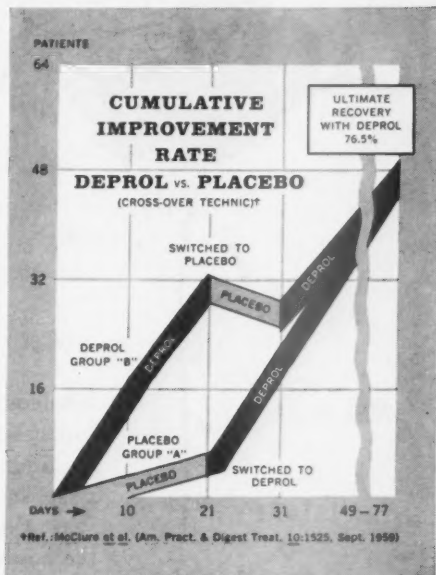
**For cardiovascular and G.I. patients —  
a smooth, balanced action that lifts depression  
as it calms anxiety...rapidly and safely**

**Balances the mood — no "seesaw" effect of amphetamine-barbiturates and energizers.** While amphetamines and energizers may stimulate the patient — they often aggravate anxiety and tension. And although amphetamine-barbiturate combinations may counteract excessive stimulation — they often deepen depression.

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

**Acts swiftly — the patient often feels better, sleeps better, within two or three days.** Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly — often within two or three days.

**Acts safely — no danger of hypotension or liver damage.** Deprol does not cause liver toxicity, hypotension, tachycardia, jitteriness, vomiting, constipation or psychotic reactions frequently reported with other antidepressant drugs. It can be safely administered with basic therapy.



Results of a controlled study of 128 patients conducted by General Practitioners, Internists, Gastroenterologists, Urologists, Surgeons, Proctologists and others in collaboration with Psychiatrists.

## Deprol®

**Dosage:** Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

**Composition:** 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

**Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.



WALLACE LABORATORIES / New Brunswick, N. J.

#### BIBLIOGRAPHY (11 clinical studies, 764 patients):

- Alexander, L. (35 patients): Chemotherapy of depression — Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958.
- Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959.
- Bell, J. L., Tauber, H., Soniy, A. and Fulvio, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:265, June 1959.
- Bratner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959.
- Landman, M. E. (50 patients): Choosing the right drug for the patient. Submitted for publication, 1960.
- McClure, C. W., Papos, P. N., Spoor, G. S., Palmer, E., Slatery, J. J., Konoloff, S. H., Henken, E. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression—New technic and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959.
- Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959.
- Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959.
- Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959.
- Sattel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination (Deprol). Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960.
- Splitter, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

The squeeze of modern diuretics  
eliminates excess fluids — but loss  
of potassium is unavoidable

***It must be replaced.***

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elixir

(Potassium Gluconate, W-T)

READILY  
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REMARKABLY  
WELL TOLERATED

EXTREMELY  
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AVOIDS  
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TABLETS AND  
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POTASSIUM



A tablespoonful of KAON Elixir twice daily (30 cc.) supplies the approximate normal daily potassium requirement (40.0 mEq.) — is approximately equal to the elemental potassium in one fourth gallon of orange juice. One teaspoonful (5 cc) approximately equals the potassium in 0.5 Gm. of potassium chloride.

**WITH ADRENAL CORTICOID THERAPY,  
KAON IS USEFUL IN PREVENTING  
POTASSIUM DEPLETION.**

*References:* W. J. Kolff, "Acute Renal Failure: Causes and Treatment," *The Medical Clinics of North America*, 30:1052 (July 1955).  
Peter Forsham, "Symposium on Adrenal Corticoid Therapy," *Metabolism*, 7:19 (Jan. 1958).

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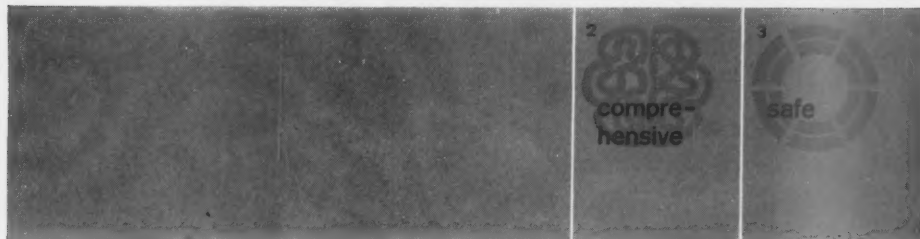
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**Nembutal®**  
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\*Nembutal rapidly produces cerebral depression of any desired degree, depending upon the dose.



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the indication: prostatitis

the incidence: "amazingly high"—"Inflammations of the prostate gland... occur with an amazingly high incidence in general practice."

the inference: probably "the most common chronic infection in men over 40 years of age."

**the ideal:**  
**"by far the most**  
**effective drug"**

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brand of nitrofurantoin

"... by far the most effective drug to be employed, and this has been substantiated in practice. It is a drug of low toxicity and, what is more important, bacteria rarely if ever become resistant to it. It can be employed for long periods of time, is bactericidal and does not favor the appearance of monilial infections."<sup>3</sup>

**In acute prostatitis:** "Antibacterial medication, preferably FURADANTIN (Eaton) 100 mg. 4 times daily is indicated..."<sup>4</sup>

**In chronic prostatitis:** "From clinical observation we have found that more cases of chronic prostatitis respond to FURADANTIN than to any other anti-infection agent."<sup>5</sup>

**In benign prostatic hypertrophy** (to prevent or treat concomitant infection): "Nitrofurantoin [FURADANTIN] may be used for protracted periods for the suppression of infection in the urinary tract, even in the presence of probable obstruction... it may provide prolonged relief from symptoms and permit better selection of the proper time for surgical or manipulative procedures."<sup>6</sup>

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**Supplied:** Tablets, 50 and 100 mg., Oral Suspension, 25 mg. per 5 cc. tsp.

**References:** 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957.  
2. Farman, F., and McDonald, D. F.: Brit. J. Urol. **31**:176, 1959. 3. Sanjurjo, L. A.: Med. Clin. N. America **43**:1601, 1959. 4. Barnes, R. W.: Prostatitis, *In* Conn, F.: Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957. 5. Barnes, R. W., in discussion of Chinn, J., and Bischoff, A. J.: Tr. West. Sect. Am. Urol. Ass. **22**:189, 1955. 6. Jawetz, E.: A.M.A. Arch. Int. M. **100**:549, 1957. 7. Glazier, M., and Lombardo, L. J., Jr.: From the film *Retropubic Prostatectomy*, Eaton Laboratories, Norwich, N. Y., 1959.

EATON LABORATORIES, NORWICH, NEW YORK





## now artificial dialysis right in the patient's room

Intermittent peritoneal dialysis with Peridial "...eliminates the need for special personnel and elaborate equipment as in the operation of an artificial kidney."\* The patient's peritoneum is utilized as a dialyzing membrane through which filterable wastes pass into the dialyzing solution—Peridial—and are removed through a special abdominal catheter.

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\*Maxwell, M. H., et al.: J.A.M.A. 170:917, 1959

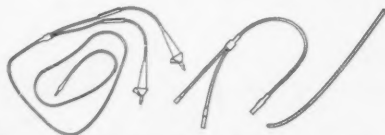
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Sodium	140 mEq./l.
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Magnesium	1.5 mEq./l.
Chloride	102 mEq./l.
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IN TWO  
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**Milpath-400** — Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

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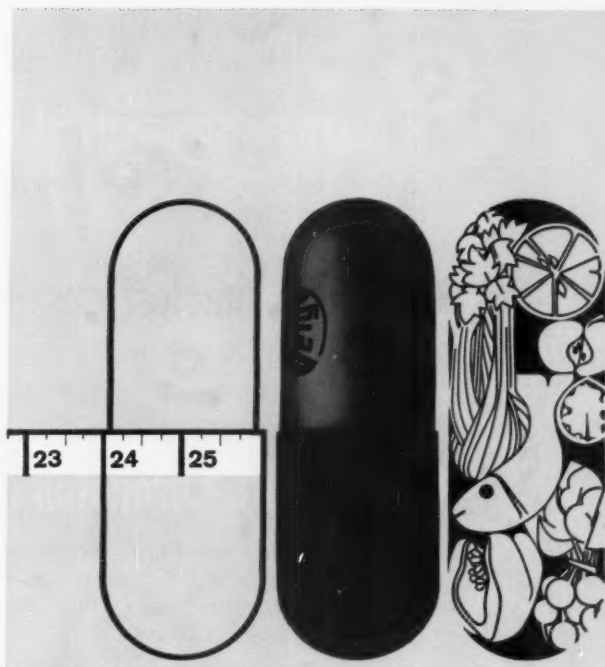
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brand of phenmetrazine HCl with vitamins and minerals

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With Prelu-Vite, as with Preludin, a weight loss 2-5 times that obtainable by dietary restriction alone, is readily achieved without the occurrence of annoying side reactions.



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**Availability:**

Prelu-Vite<sup>®</sup> Capsules, each containing 25 mg. of Preludin (brand of phenmetrazine HCl) with vitamins A, B, C and D and 5 minerals.

Under license from C. H. Boehringer Sohn, Ingelheim.

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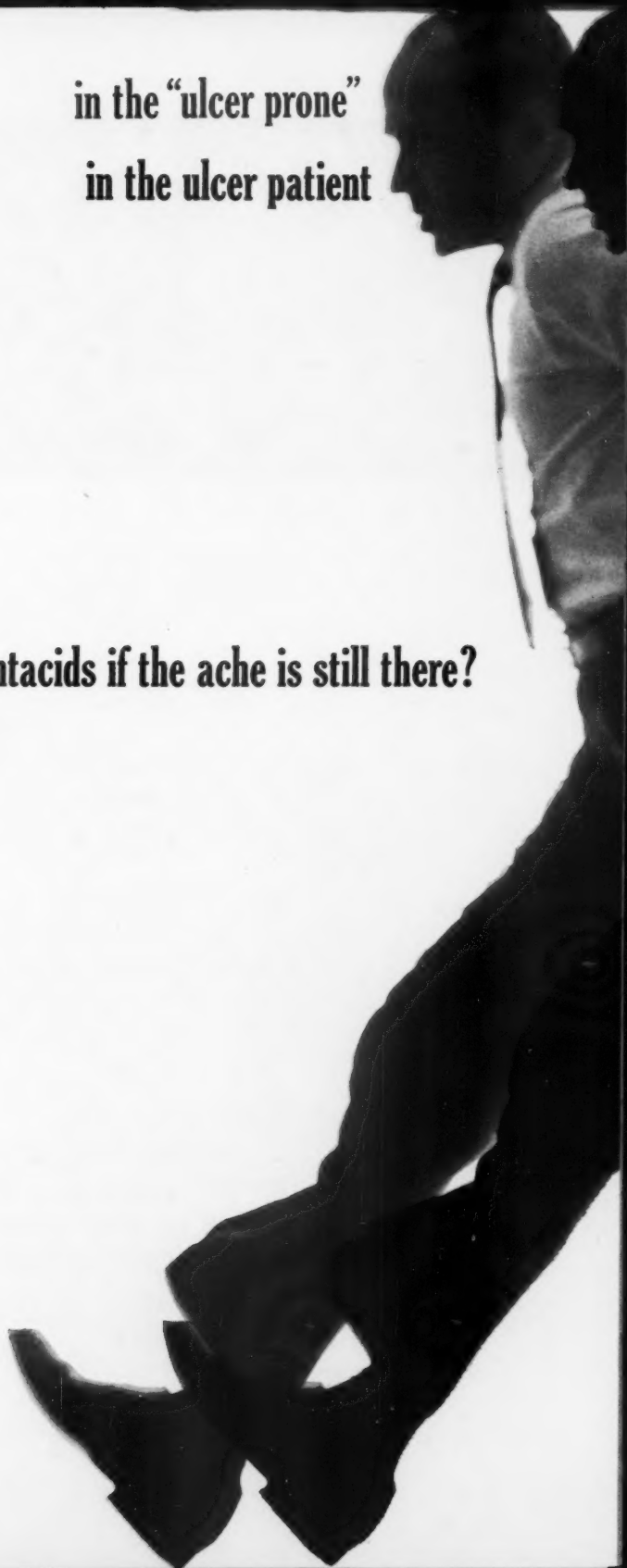
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**in the "ulcer prone"  
in the ulcer patient**

**...what good are antacids if the ache is still there?**





# Kolantyl

**much more than an antacid  
blocks all three sources of  
pre-ulcer and ulcer pain**

Antacid relief is only partial, because acid causes only part of your patient's discomfort. In almost every case, he suffers with painful G. I. spasm, too.

Kolantyl stops it. Of course, most antacids will soothe irritated mucosa.

Kolantyl, however, does more... helps prevent further erosion, promotes healing. And when you prescribe Kolantyl, your patients will take it gladly. You see, Kolantyl tastes extra good.

**Dosage:** 1 tablespoonful or  
2 tablets, every three  
hours, as needed.

**Formula:** Each tablet or 10 cc. Gel  
(2 teaspoonfuls) contains:

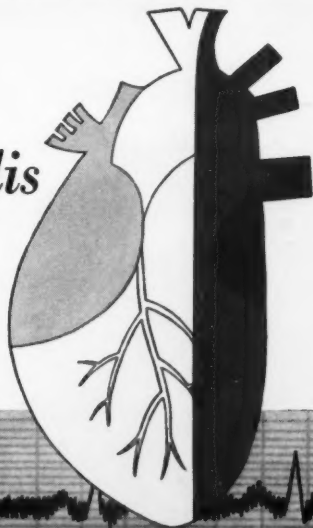
Bentyl (dicyclomine) Hydrochloride	5 mg.
Aluminum Hydroxide Gel, Dried	400 mg.
Magnesium Oxide, Heavy	200 mg.
Sodium Lauryl Sulfate	25 mg.
Methylcellulose	100 mg.

TRADEMARKS: BENTYL®, KOLANTYL®

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*whenever digitalis  
is indicated*



# 'LANOXIN'<sup>®</sup> brand DIGOXIN

*formerly known as Digoxin 'B. W. & Co.'*

*"If one digitalis agent were  
to be recommended for its  
adaptability to the many and  
varied clinical contingencies,  
we believe Digoxin would be  
the drug of choice."*

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy.  
Boston, Little, Brown & Company, 1954, p. 23, par. 2.

**'LANOXIN' TABLETS**

0.25 mg. scored (white)

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**'LANOXIN' INJECTION**

0.5 mg. in 2 cc. (I.M. or I.V.)

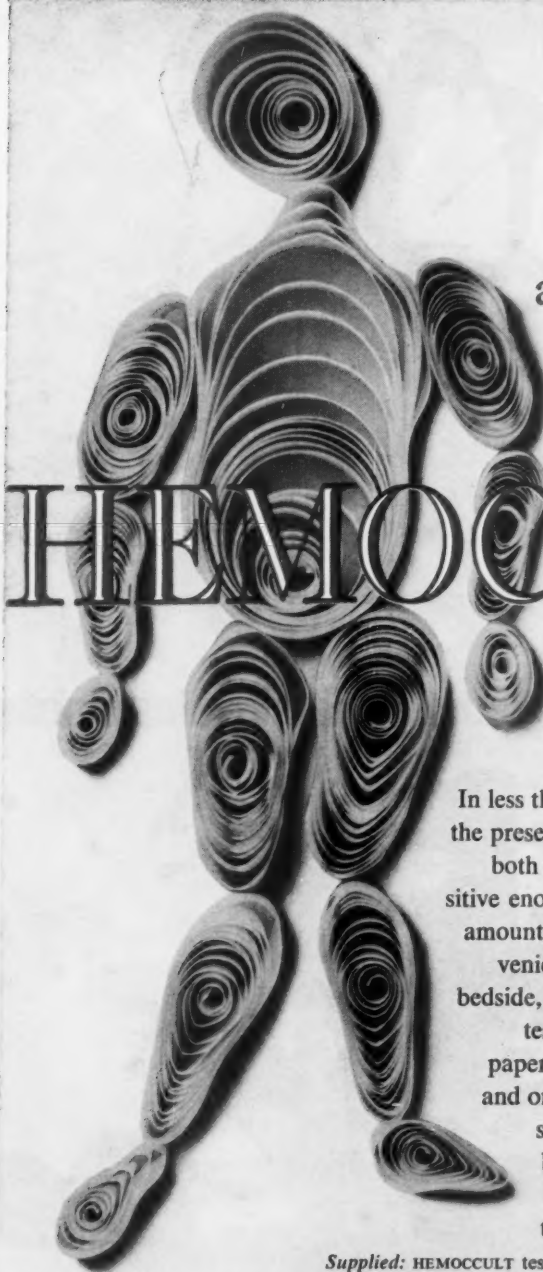
**'LANOXIN' ELIXIR PEDIATRIC**

0.05 mg. in 1 cc.



**BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.**





a single test  
accurately detects  
occult blood  
in 1 minute

# HEMOCCULT<sup>TM</sup>

completes  
the diagnostic  
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*Supplied:* HEMOCCULT test kit contains a roll of guaiac-impregnated test paper for 100 tests in plastic dispenser, one 10 ml. plastic bottle of developer and directions for use. All in compact carrying case.

*Literature available on request.*



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# NEW **LIBRIUM**

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## THE SUCCESSOR TO THE TRANQUILIZERS

**successor in specificity:** relieves anxiety, agitation and tension, and liberates the patient from destructive fears.

**successor in safety:** not encumbered by depression, lacks autonomic or extrapyramidal side effects.

**successor in versatility:** covers the entire meprobamate area of therapy plus a significant portion of the phenothiazine area plus the difficult middle ground between the two.

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**Published reports on Librium:** 1. T. H. Harris, *Dis. Nerv. System*, 21:(Suppl.), 3, 1960. 2. L. O. Randall, *ibid.*, p. 7. 3. J. M. Tobin, I. F. Bird and D. E. Boyle, *ibid.*, p. 11. 4. H. A. Bowes, *ibid.*, p. 20. 5. J. Kinross-Wright, I. M. Cohen and J. A. Knight, *ibid.*, p. 23. 6. H. H. Farb, *ibid.*, p. 27. 7. C. Breitner, *ibid.*, p. 31. 8. I. M. Cohen, *Discussant, ibid.*, p. 35. 9. G. A. Constant, *ibid.*, p. 37. 10. L. J. Thomas, *ibid.*, p. 40. 11. R. C. V. Robinson, *ibid.*, p. 43. 12. S. C. Kaim and I. N. Rosenstein, *ibid.*, p. 46. 13. H. E. Ticktin and J. D. Schultz, *ibid.*, p. 49. 14. J. N. Sussex, *ibid.*, p. 53. 15. I. N. Rosenstein, *ibid.*, p. 57. 16. D. C. English, *Curr. Therap. Res.*, 2:88, 1960. 17. T. H. Harris, *J.A.M.A.*, 172:1162, 1960. 18. G. L. Usdin, *J. Louisiana M. Soc.*, 112:142, 1960. 19. I. N. Rosenstein and C. W. Silverblatt, paper read at Pan American Medical Association, 35th Anniversary Congress, Mexico City, Mexico, May 2-11, 1960. 20. K. Rickels, *ibid.* 21. N. Toll, *Dis. Nerv. System*, 21:264, 1960.

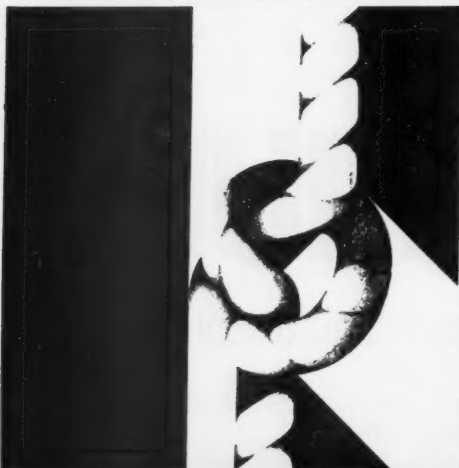
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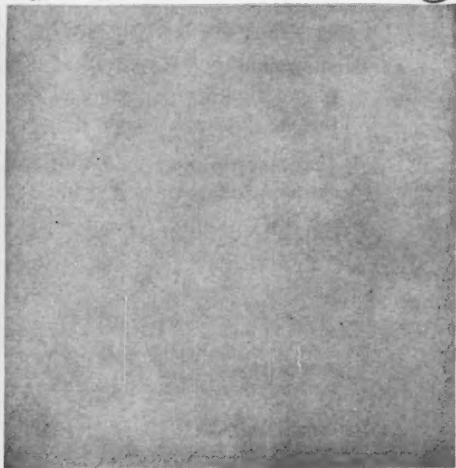


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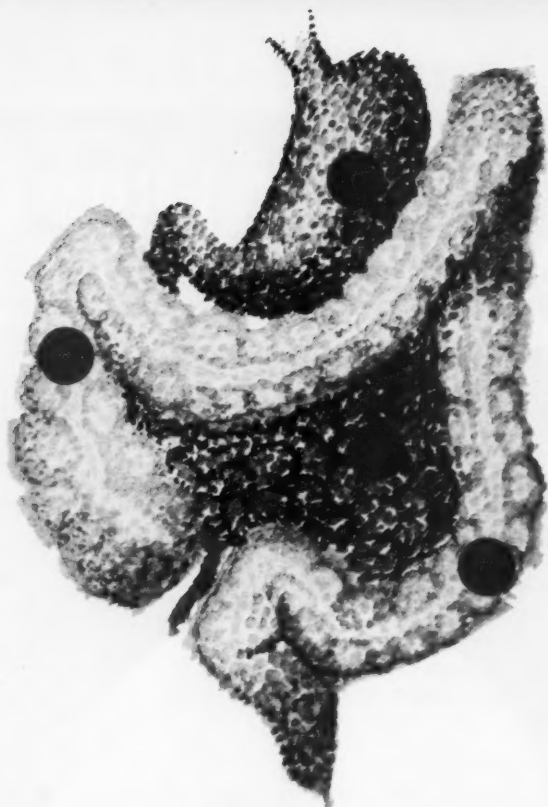
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1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

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- (1) Winkelstein, A.: *Am. J. Gastroenterol.* 27:45-52 (Jan.) 1957. (2) Brown, C. H.: *Am. Pract. & Digest Treat.* 9:405-411 (March) 1958. (3) Winkelstein, A., and Schweiger, E.: *J.A.M.A.* 160:1111-1113 (March 31) 1956.



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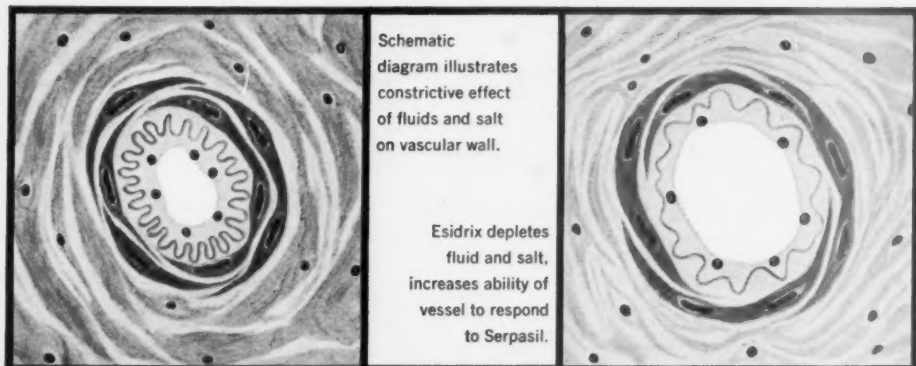
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1. Selzer, A. and Ryland, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.



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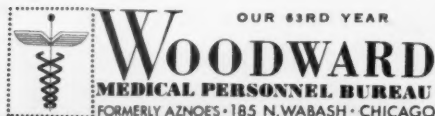


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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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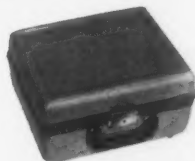
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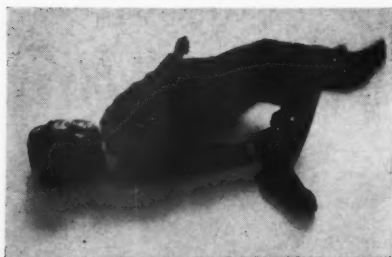
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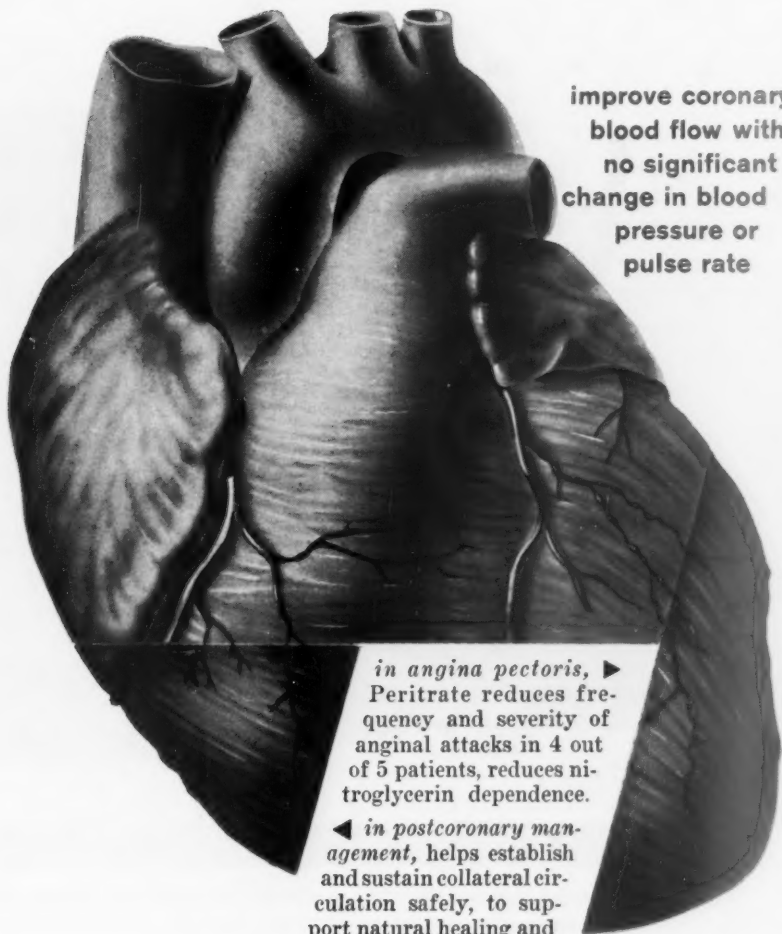
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1. Forster, F. M.: *Wisconsin M. J.* 58:375 (July) 1959. 2. Meyer, J. S.: *M. Times* 87:743 (June) 1959. 3. Lambros, V. S.: *Dis. Nerv. System* 19:349 (Aug.) 1958. 4. Niswander, G. D., and Karacan, I.: *Am. J. Psychiat.* 116:260 (Sept.) 1959. 5. Carter, C. H.: *Dis. Nerv. System* 21:50 (Jan.) 1960.

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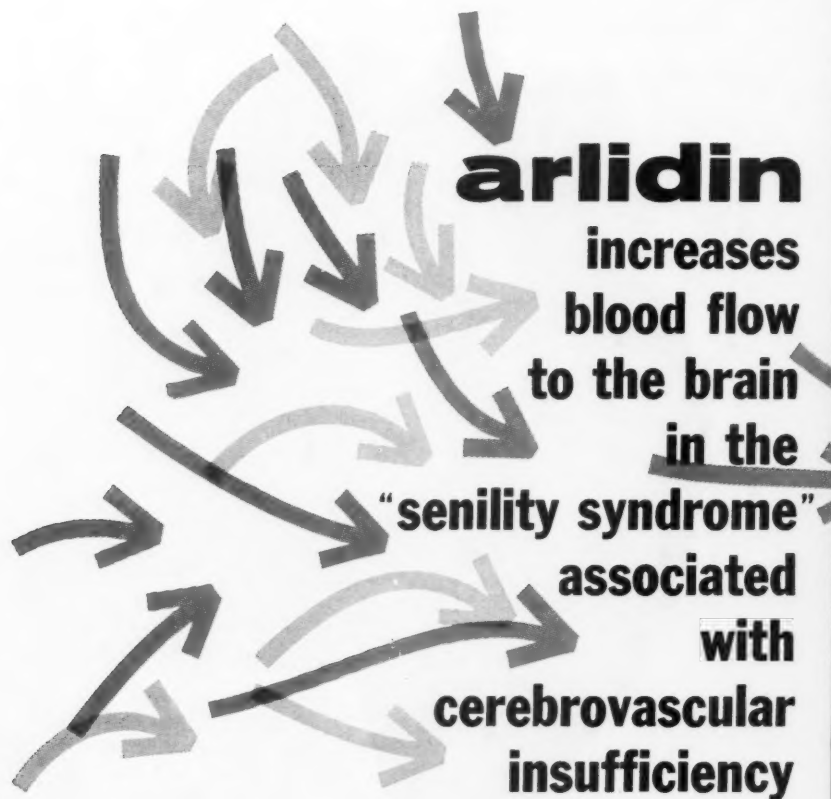
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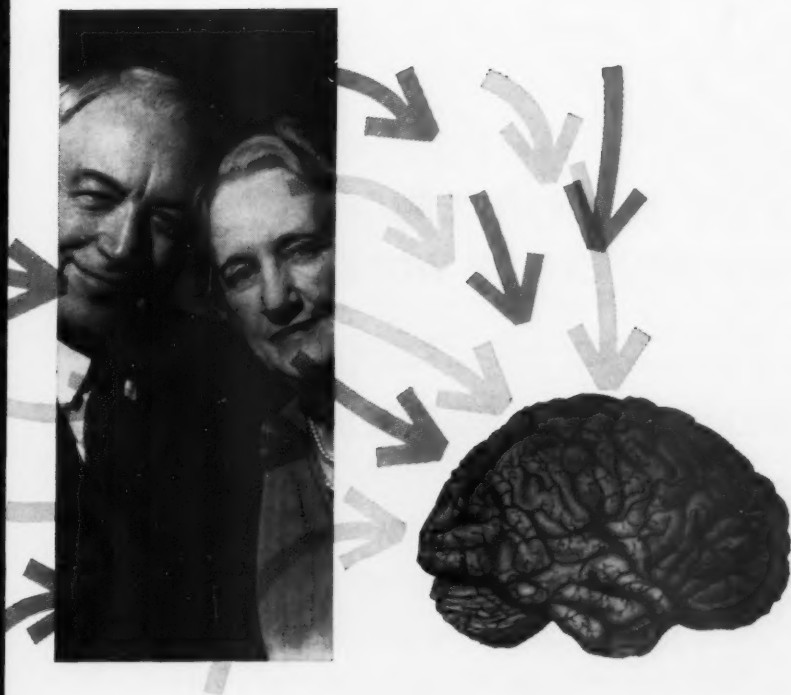


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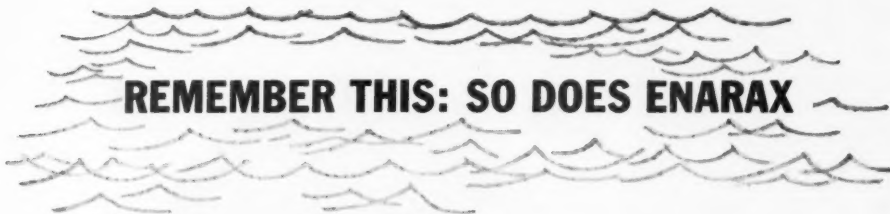
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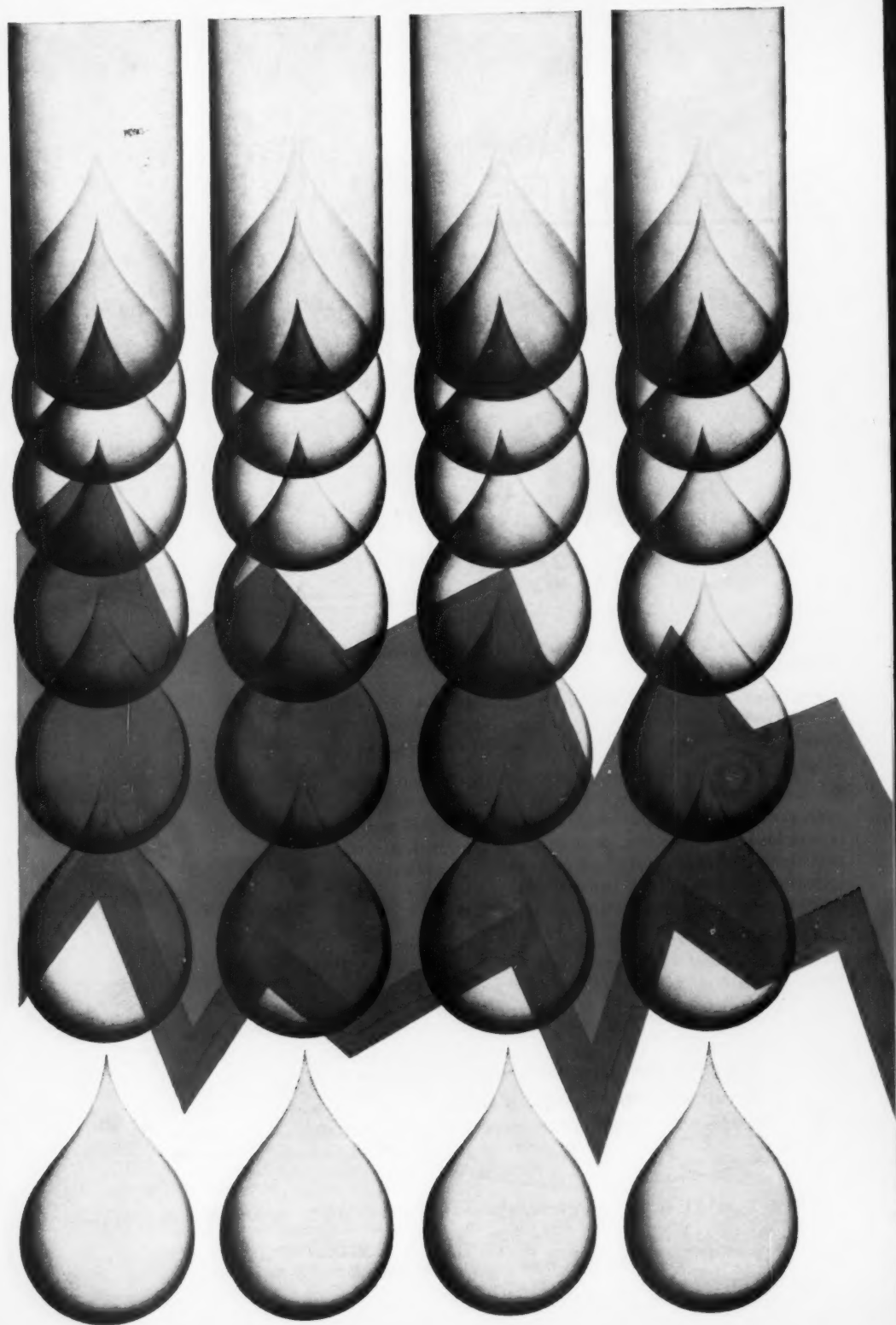
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1. Stenger, E. G. et al.: Schweiz. med. Wchnschr. 89:1126, 1959.
2. Fuchs, M. et al.: Current Therap. Research 2:11, Jan. 1960.
3. Reutter, F. and Schaub, F.: Schweiz. med. Wchnschr. 89:1138, 1959.
4. Veyrat, R. et al.: Schweiz. med. Wchnschr. 89:1133, 1959.
5. Ford, R. V.: Manuscript submitted for publication.
6. Analysis of Case Reports Compiled by Biostatistical Dept. of Geigy Pharmaceuticals.
7. Bryant, J. M.: Report to Geigy Pharmaceuticals.

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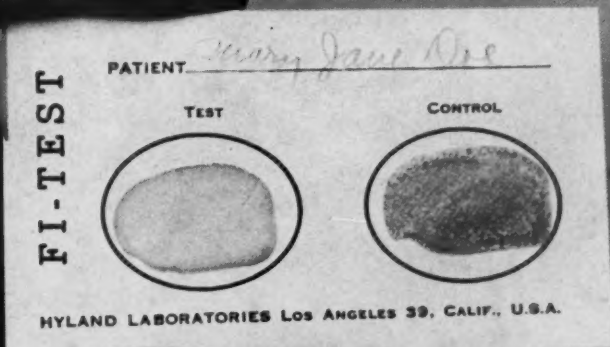


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References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Friend, D. H.: Clin. Pharm. & Therap. 1:5 (Mar.-Apr.) 1960. 3. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

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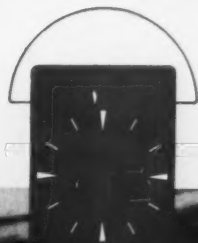
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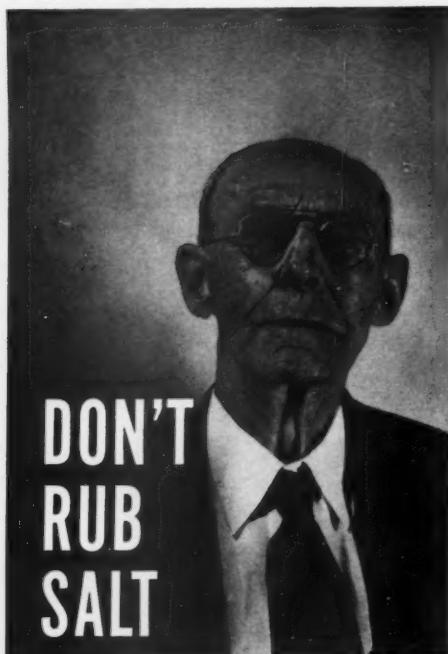
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(1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956. (2) Cass, L. J. and Frederik, W. S.: Jnl. Lancet, 73: 414-416, 1953. (3) Marshall, W.: So. Dak. J. Med. & Pharm. 8:151-153, 1955.

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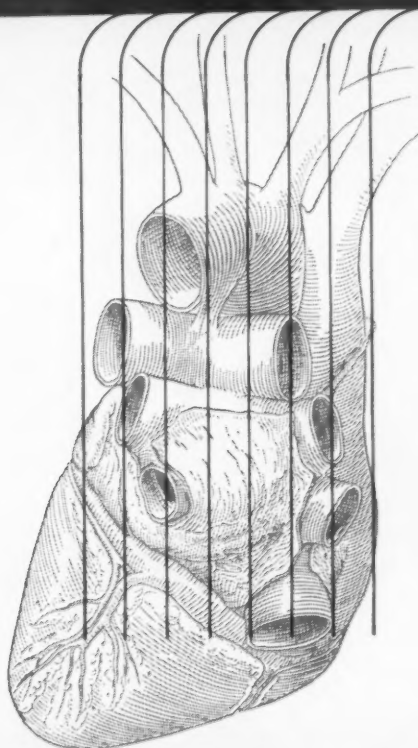
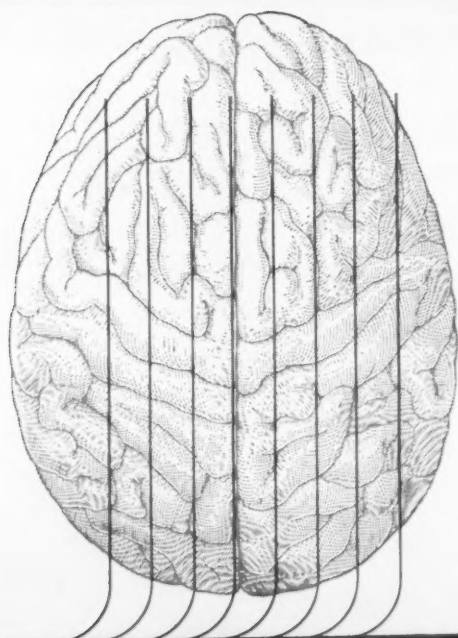
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*Selected bibliography from 38 published papers:* 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, *Virginia M. Month.*, 87:23, 1960. 4. C. C. Griffith, *Clin. Med.*, 6:1555, 1959. 5. C. C. Griffith, *Dis. Nerv. System*, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, 20:(Suppl.), 26, 1959.

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	19-23	26-30	1-4	5-9	12-16	19-23	26-30	2-6	9-13	15-20	23-27	Jan. 30-Feb. 3	9-10	13-17	20-24
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<b>Course No. 1, THE PLACE OF HEMATOLOGY IN INTERNAL MEDICINE: WITH AN INTRODUCTION TO RADIOISOTOPE TECHNIQUES AND THEIR APPLICATION:</b> The Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director.															
<b>Course No. 2, CANCER AND THE INTERNIST—1960 CONCEPTS:</b> Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N. Y.; Rulon W. Rawson, M.D., F.A.C.P., Director		X													
<b>Course No. 3, THE PHYSIOLOGIC BASIS OF ELECTROCARDIOGRAPHY:</b> University of Utah College of Medicine, Salt Lake City, Utah; Hans H. Hecht, M.D., F.A.C.P., Director.			X												
<b>Course No. 4, RECENT ADVANCES IN DRUG THERAPY:</b> University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.															
<b>Course No. 5, MECHANISMS OF DISEASE:</b> Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.									X						
<b>Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE:</b> The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.															X

The following courses are scheduled for Spring, 1961: CARDIOVASCULAR DISEASES, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6-10; INTERNAL MEDICINE, McGill University, Ronald V. Christie, M.D., F.A.C.P., Director, March 13-17; ADVANCED CLINICAL ELECTROCARDIOGRAPHY, The University of Virginia, William Parson, M.D., F.A.C.P., Director, March 23-25; PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, April 12-15; GASTROENTEROLOGY, University of Pennsylvania School of Medicine, Henry L. Bockus, M.D., F.A.C.P., Director, May 15-19; CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19-23.



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(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

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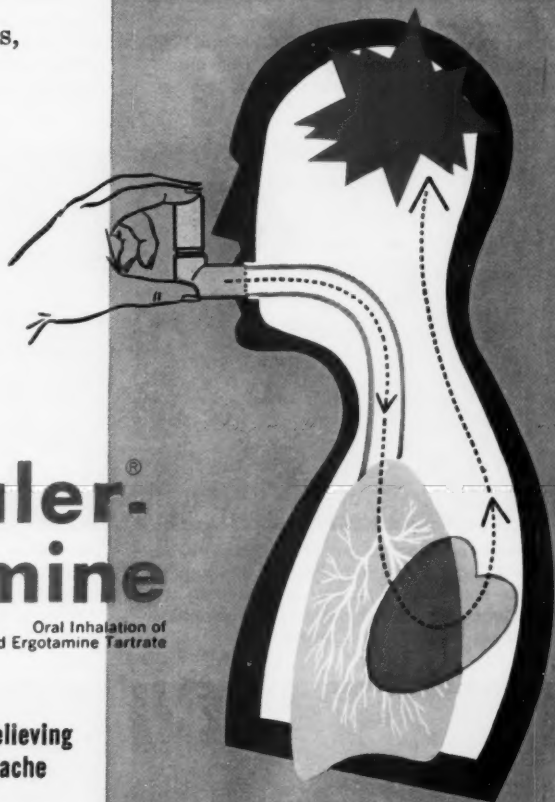
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## \*IMPORTANT NOTICE

On October 1, 1960, the Baltimore Editorial Office of the ANNALS OF INTERNAL MEDICINE will close. After this date the new address will be—

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